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VOLUME 99(1) — JANUARY 1990

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

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SUPRAGLOTTIC CARCINOMA: PATTERNS OF RECURRENCE

EVALUATION OF AMINO-OXYACETIC ACID AS A PALLIATIVE IN TINNITUS

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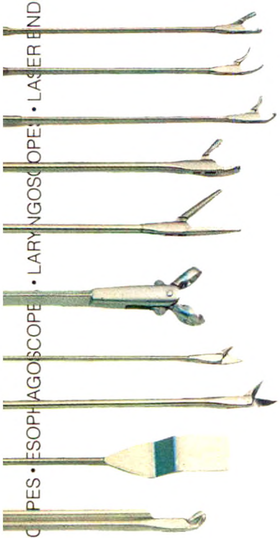

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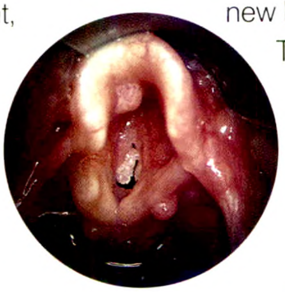

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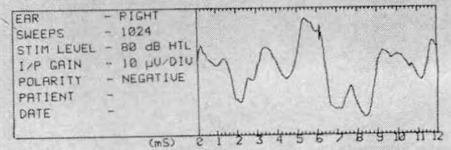
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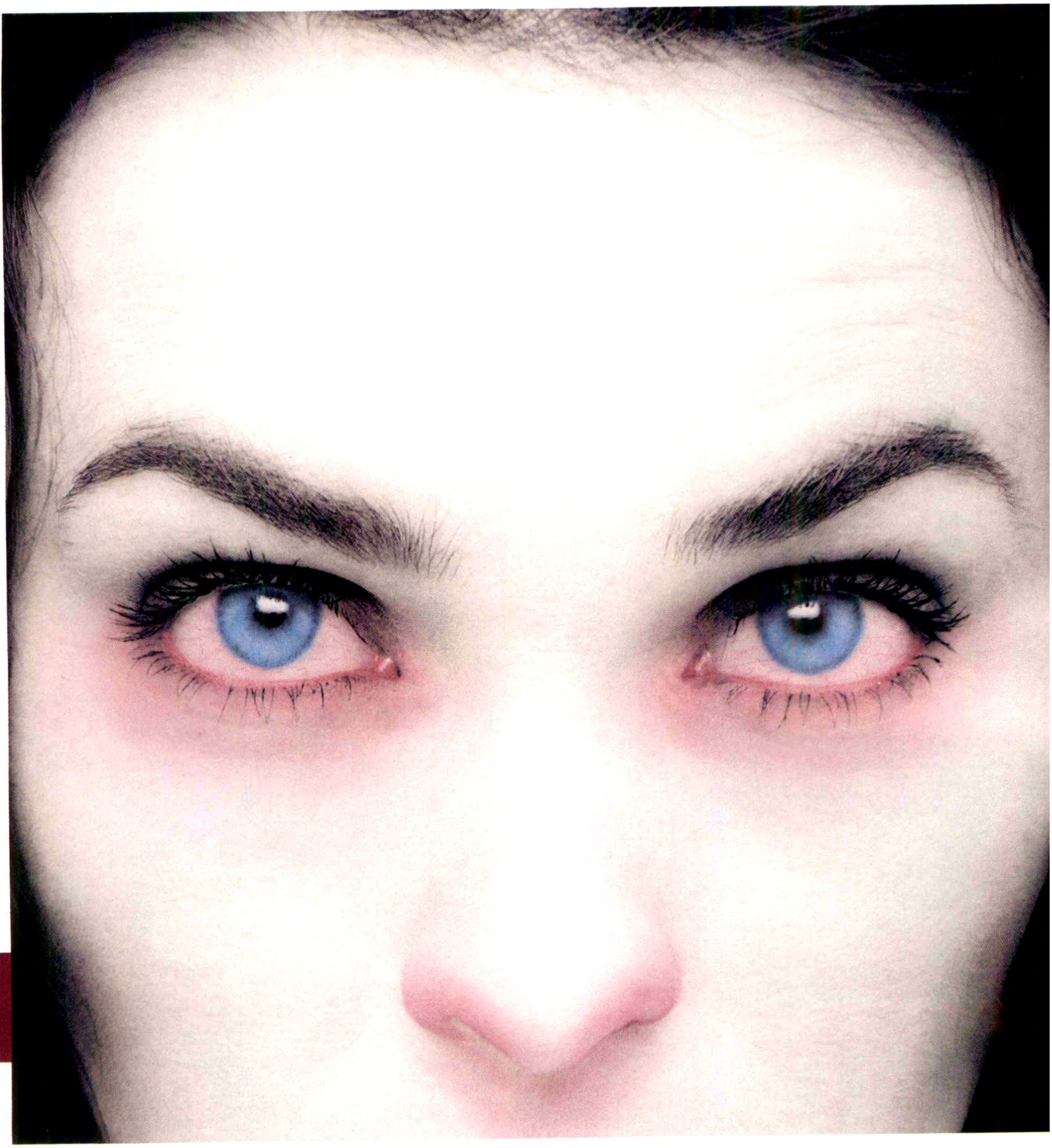

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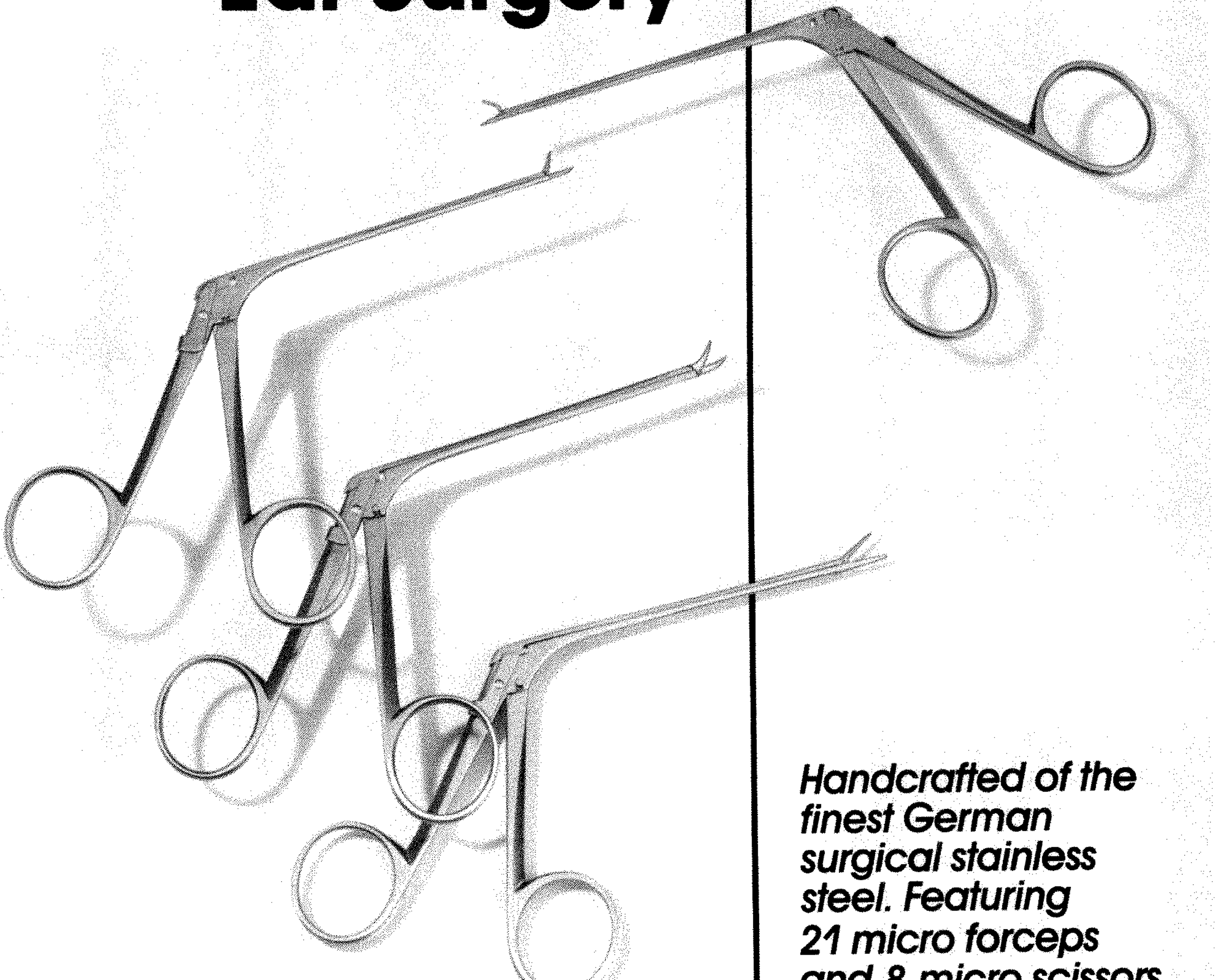

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Ann Otol Rhinol Laryngol 99:1990

CALIBRATED APPROACH TO ENDOSCOPIC SINUS SURGERY

FRANK E. LUCENTE, MD PHILIP S. SCHOENFELD, MD
NEW YORK, NEW YORK

Endoscopic sinus surgery, in which the surgeon views the nose and paranasal sinuses through a telescope, can potentially lead to loss of perspective of the patient's entire head. Preoperative computed tomographs are also taken at angles different from those encountered in the surgical setting. As a result, the appropriate angle and depth of instrument insertion can fail to be appreciated. In order to study those angles and depths in a setting that more closely resembles the clinical situation in the operating room, we have performed 15 cadaver dissections and measured 14 dimensions relevant to the endoscopic approach. We recommend that cadaver dissection be an important part of continued training in sinus surgery. We also recommend that a reference probe be placed along the floor of the nose and that endoscopic instruments be calibrated at 1-cm intervals so that the depth of insertion can be monitored by an observer or instructor.

KEY WORDS — sinus anatomy, sinus surgery.

The recent flurry of interest in endoscopic sinus surgery has posed a new challenge to the surgeon who has traditionally operated in the nose and paranasal sinuses while simultaneously keeping the patient's entire head in view so that the angle and depth of instrument insertion can be appreciated.[1,2] The endoscopic approach, in which the surgeon's vision is focused through a monocular telescope, can conceivably lead to loss of perspective, and despite the best possible radiographic delineation of anatomy, complications may ensue.

After observing several such complications, the senior author (F.E.L.) was reminded of the statement of Mosher, who in 1929 wrote,

> If the ethmoid labyrinth was placed in any other part of the body it would be an insignificant and harmless collection of bony cells. Placed where Nature has put it, it has a number of major relationships so that diseases and surgery of the labyrinth often lead to tragedy. It has been said that the ethmoidal operation is the easiest in surgery. So it is to the operator who lacks a surgical conscience. Theoretically, the operation is easy. In practice, however, it has proved to be one of the easiest operations with which to kill a patient.[3(p869)]

Mosher believed that unless exquisitely familiar with the anatomy, one should not operate on the ethmoid sinus because of its proximity to the brain and the orbit. However, textbooks do not adequately prepare the surgeon for this task because of the variability and inaccuracy of the drawings available in even the most respected texts devoted to paranasal sinus surgery.

Successful surgery is predicated on a meticulous knowledge of anatomy, and that anatomy is probably best learned in the gross dissection laboratory, as well as in the numerous courses now offered. In order to demonstrate the feasibility of that exercise and to review the variations of sinus anatomy that might confound the surgeon, we have made calibrated anatomic studies of cadavers and assessed landmarks of importance to the endoscopic sinus surgeon.

MATERIALS AND METHODS

Fifteen cadavers were used for a total of 30 sets of measurements. The series consisted of seven white women, five white men, two black women, and one black man. Each skull was sagittally bisected. The septum was removed from each bisected skull, and the most medial structures on each side were identified.

The measuring instruments consisted of a transparent protractor calibrated in degrees and a tape measure calibrated in millimeters. Each measurement was made by placing the origin of the protractor at the pyriform aperture and aligning the 0° angle with the floor of the nose just anterior to the base of the anterior nasal spine. By placing the tape measure at the pyriform aperture on top of the protractor, it was possible to ascertain both the angle from the floor of the nasal cavity and the distance from the pyriform aperture of the structure being studied (Fig 1). The pyriform aperture was chosen as the point of reference because the measurements originating from this point most closely approximate the distances and angles encountered in endoscopic sinus surgery (Fig 2). Each measurement was repeated to ensure accuracy.

These first measurements, taken before any further dissection was performed, included distance and angle to the anteriormost, middle, and posteriormost ethmoid air cells, posterior pharyngeal wall, eustachian tube ostium, ethmoid bulla, and hiatus semilunaris. Next, the inferior, middle, and superior turbinates were removed with scalpel and forceps, and the distance and angle to the maxillary

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Presented at the meeting of the American Laryngological Association, San Francisco, April 1-2, 1989.

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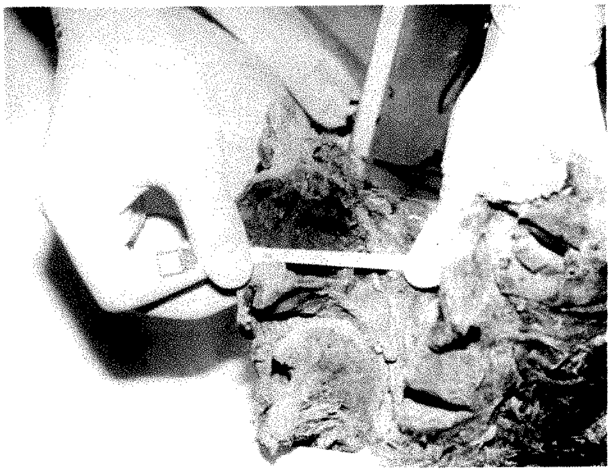

Fig 1. Sagittal section of dried skull demonstrating manner in which measuring probes were inserted in cadaver heads to measure distances and angles with regard to reference probe along floor.

sinus ostium and nasolacrimal duct orifice were measured.

Following the unciform groove, the embryologic slit between the uncinate process of the ethmoid and the ethmoid bulla, we attempted to locate the frontal sinus ostium. Finally, using Takahashi forceps, we removed all ethmoid air cells through the ethmoid bulla to the lamina papyracea. This provided access to the depth of the ethmoid labyrinth. Measurements were also taken of the sphenoid sinus and of the posterior sphenoid sinus wall. All skulls were studied with the dissector standing above and the skull placed in a position that simulated that of the patient's head during endoscopic sinus surgery.

RESULTS

The Table shows the angle and length of the particular measurements that were recorded in terms of the mean with the range of all specimens measured. For further comparison and interpretation, the results are reported according to the gender of the cadavers used. There was no significant difference in measurements between our white and black cadavers.

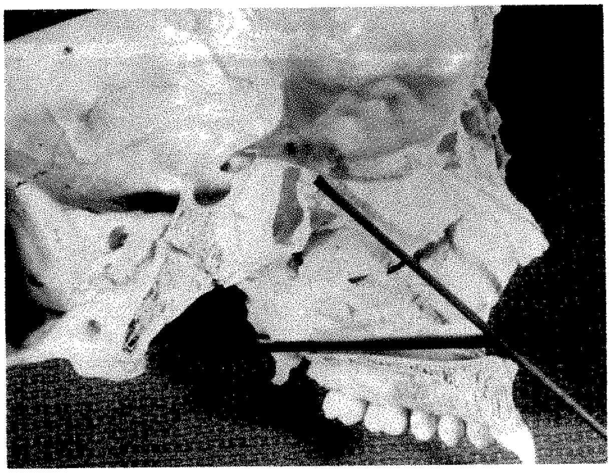

Fig 2. Demonstration of sagittally sectioned skull with sample measurement being taken from nasal spine to posterior pharyngeal wall in fashion similar to that in which measurements were taken in cadaver heads in this study.

MEAN DISTANCE FROM PYRIFORM APERTURE AND MEAN ANGLE FROM FLOOR OF NASAL CAVITY

	Men		*Women*	
Structure	*Distance (cm) ±0.2 cm*	*Angle ±4°*	*Distance (cm) ±0.2 cm*	*Angle ±4°*
Superior extent of anterior ethmoid sinus	5.2	77	5.1	81
Superior extent of mid-portion of ethmoid sinus	5.5	63	5.4	64
Superior extent of posterior ethmoid sinus	5.8	51	5.8	49
Depth of ethmoid labyrinth	6.0	32	6.5	39
Hiatus semilunaris	3.9	45	3.8	51
Ethmoid bulla	3.9	57	3.9	60
Maxillary sinus ostium	3.6	37	3.4	48
Nasolacrimal duct	2.3	59	2.4	64
Frontal sinus ostium	4.6	78	4.9	81
Sphenoid sinus ostium	5.5	41	5.6	42
Posterior sphenoid face	7.4	32	7.8	36
Height of nasal cavity	4.3	NA	4.6	NA
Posterior pharyngeal wall	7.2	NA	7.4	NA
Eustachian tube ostium	5.8	8	5.9	10

NA — not applicable.

DISCUSSION

Our knowledge of the anatomy of the sinuses has evolved as interest in the surgery of the sinuses has increased. Prehistoric physician-priests learned the benefits of trephination of frontal sinuses to relieve pain, and Hippocrates reported relief of nasal obstruction by avulsion of polyps. Well known are the contributions of Highmore, who elucidated the anatomy of the maxillary antrum; Schneider, who described the secretory properties of nasal mucous membranes; Fallopius, who used a wire snare to remove polyps; and Caldwell, Luc, Spicer, Ogston,

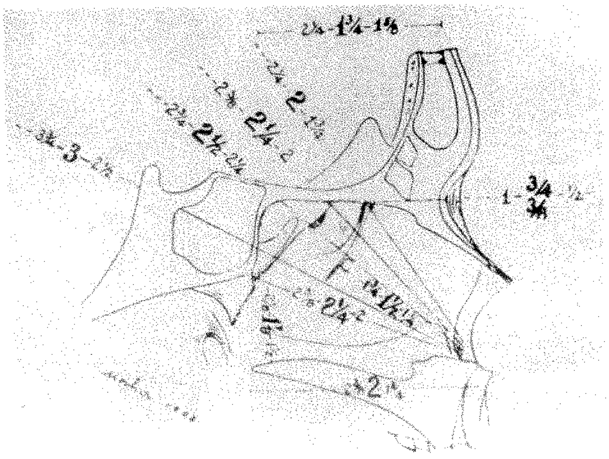

Fig 3. Line drawing from classic anatomic study of nasal cavity dimensions. (Reprinted from Mosher.[3])

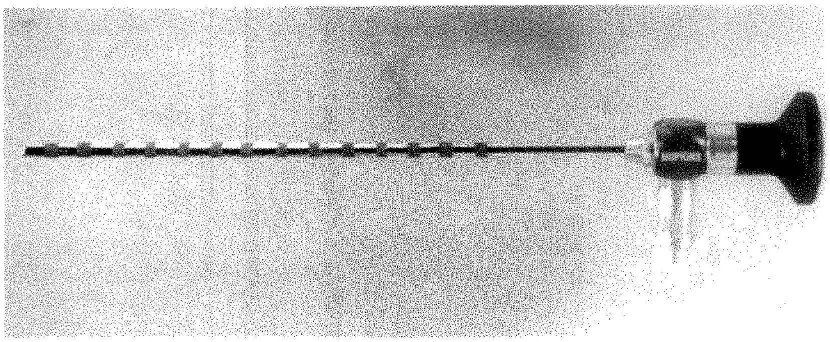

Fig 4. Rigid nasal endoscope marked at 1-cm intervals to facilitate judging depth of insertion. Other distances can be measured in similar fashion.

Sluder, Lynch, and others, who designed surgical procedures still in use today.[4] Perhaps less well known is the contribution of Frankel, who in 1891 added to our knowledge of sinus anatomy by freezing cadaver heads in buckets of water and sectioning them with carpenter's saws. The meticulous anatomic studies of the ethmoid sinuses by Mosher (Fig 3)[3] and his contemporaries are seldom cited in recent years, in which attention has focused on the rapid evolution of radiographic diagnostic techniques[5,6] that has allowed us to move from plain radiography to polytomography, xeroradiography, computed tomography, and magnetic resonance imaging; and yet, knowledge of clinical surgical anatomy remains of paramount importance.

The CT has probably become the most widely used diagnostic tool for the evaluation of sinus disease. Good-quality axial and coronal projections are helpful in identifying the location of disease itself, but both cuts deviate approximately 20° to 30° from the view obtained by the surgeon standing or seated above the patient whose head is placed in the surgical position. As a result, the surgeon who expects the distances and dimensional angles found on the CT will be misled when viewing the sinuses through a monocular telescope.

The labyrinthine nature of the ethmoid base is well known, and the dissections confirmed the presence of numerous thin-walled aerated cells that are small and multiple anteriorly and large and sparse posteriorly.[7] Other than the strong anterior boundary, namely the posterior surface of the ascending process of the maxilla, the walls of the ethmoid labyrinth are thin and easily perforated. Anterior cells were encountered in our specimens as close as 4.2 cm to the base of the nasal spine, and posterior cells occurred as deep as 7.5 cm. The deeper the instruments are inserted, the more the angle of insertion must be reduced, from approximately 75° or 80° anteriorly to 30° or 40° posteriorly, in order to avoid perforation of the lamina papyracea or cribriform plate and damage to the posterior ethmoid vessels or optic nerve.

The posterior boundary of the ethmoid labyrinth is the anterior face of the sphenoid sinus. In its upper portion the sphenoid sinus ostium can be found. As this boundary is traversed, the surgeon should not only decrease the angle of instrument insertion from 50° to 40°, but also respect the lateral bony walls, which overlie several cranial nerves and the internal carotid artery.

The posterior wall of the sphenoid sinus is the furthest structure in the nasal cavity from the pyriform aperture, averaging 7.4 to 7.8 cm from the anterior spine. The endoscopic surgeon who wishes to enter the sphenoid sinus must insert the instruments a considerable distance in order to be actually within the sphenoid sinus rather than in a large posterior ethmoid cell.

Study of the measurements listed in the Table and confirmation of these distances and angles in each surgeon's dissection laboratory will provide helpful information when he or she is contemplating operating in the sinus with the limited vision provided by an endoscope. It will also allow interpretation of the axial and coronal CT scans, which are obtained at angles that do not simulate the clini-

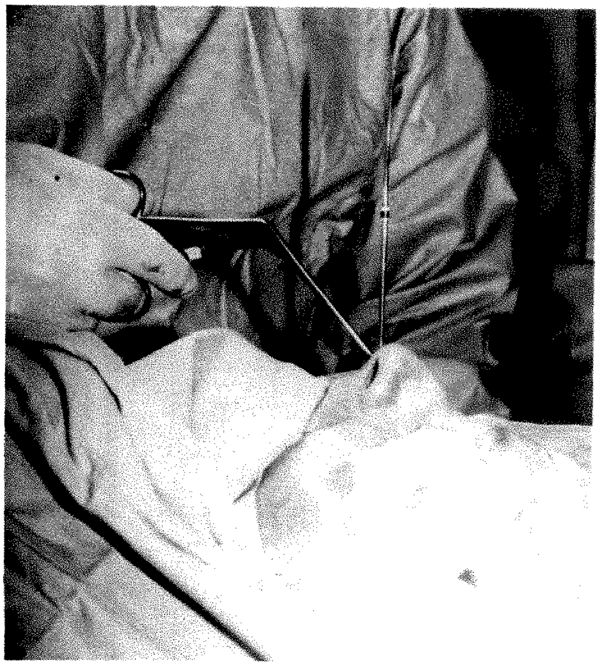

Fig 5. Patient with probe along floor of nose to act as reference line and allow observation of angle at which Takahashi forceps are inserted in nasal cavity.

cal setting, in which the standing or seated surgeon faces the supine patient.

As a final caveat to teachers and students alike, we would like to recommend that the standard sinus endoscope and rongeurs be marked at 1-cm intervals (Fig 4), that the head and eyes be visible and observed frequently, and that a reference probe be placed along the floor of the nose (Fig 5). This will allow the surgeon, the assistant, and the supervisor (in the case of resident surgery) to know the pertinent depths and angles as they enter the dark and bloody field of which Mosher spoke.

In conclusion, endoscopic sinus surgery has added a new dimension to the surgical procedures performed on the paranasal sinuses. Unfortunately, the complex and vital anatomy of this area is unforgiving to the overzealous or inexperienced endoscopist. The need for familiarity with sinus anatomy before attempting surgery cannot be overemphasized.

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NONSQUAMOUS CELL MALIGNANCIES OF THE PARANASAL SINUSES

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Nonsquamous cell malignancies represent half of paranasal sinus cancers. Since 1975, 103 patients have been treated at The Cleveland Clinic Foundation for sinus malignancies. Forty-nine patients had nonsquamous cell malignancies: 12 (25%) sarcoma, 10 (20%) adenoid cystic carcinoma, 9 (18%) adenocarcinoma, 9 (18%) lymphoma, and 9 (18%) miscellaneous tumors. Ten patients presented with T1 or T2 disease at the primary site, 16 with T3, and 23 with T4. Ten patients had primary ethmoid malignancies; the remainder of the tumors originated in the maxillary sinus. Five patients had evidence of regional or distant metastases at presentation. Twelve patients were free of disease after initial management. Three patients with recurrent disease were salvaged with additional therapy. Two patients died of complications in the immediate postoperative period. Patients with less extensive primary lesions have an improved prognosis. Survival was similar for the different histologic diagnoses.

KEY WORDS — nonsquamous cell malignancies, paranasal sinus cancer.

INTRODUCTION

This report evaluates the diagnosis, management, and long-term follow-up of 49 patients with nonsquamous cell malignancies of the paranasal sinuses who presented to The Cleveland Clinic Foundation between the years 1975 and 1988. Malignancies of the paranasal sinuses are uncommon entities; they represent 0.2% to 0.8% of all cancers and 3% of upper aerodigestive tract malignancies.[1] Approximately 80% of paranasal sinus malignancies arise from mucosa, with a large percentage represented by squamous cell carcinoma. The majority of nonsquamous carcinomas arise from the seromucous glands in the epithelium; only a small number arise from the remaining histologic contents of the sinuses.[2]

Paranasal sinus malignancies are characterized by an indolent progression, with early symptoms mimicking nonspecific sinus disease. The diagnosis of malignancy often does not become evident until extensive local invasion of the oral cavity, cheek, anterior cranial fossa, or orbit has taken place. With more advanced disease, prognosis declines precipitously despite aggressive, multimodality therapy.[3]

Nonsquamous cell malignancies of the paranasal sinuses have been poorly characterized for a number of reasons: sporadic occurrence, clumping of all sinus cancers in treatment reports, and an absence of prospective treatment protocols. This report documents the treatment of 49 patients with nonsquamous cell malignancies and examines factors that place patients at risk for treatment failure.

MATERIALS AND METHODS

A retrospective chart review was undertaken on patients with nonsquamous cell malignancies of the paranasal sinuses treated at The Cleveland Clinic Foundation between 1975 and 1988. A total of 103 patients were treated for paranasal sinus cancers, 54 with squamous cell carcinoma and 49 with nonsquamous cell malignancies.

The patients' charts were reviewed for demographic data, symptoms and pertinent physical findings on presentation, radiographic and surgical assessment, definitive therapeutic intervention, presence of tumor on final surgical margins, complications, and final treatment outcome. Clinical staging was performed retrospectively through a combination of physical examination and radiographic assessment. For the purposes of this study, ethmoid primary lesions were staged as T3 or T4 maxillary tumors,[4] according to the degree of local invasion. Similarly, patients with lymphoma were also staged according to this system, rather than the typical American Joint Committee on Cancer staging system.[4] Follow-up was conducted by telephone interview for those patients not seen in the year prior to the conclusion of the study. The Kaplan-Meier method was used to estimate survival for the

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From the Department of Otolaryngology and Communicative Disorders (Kraus, Levine, Wood, Tucker, Lavertu), and the Department of Biostatistics and Epidemiology (Medendorp), The Cleveland Clinic Foundation, Cleveland, Ohio, and the Division of Otolaryngology, University of Rochester School of Medicine and Dentistry, Rochester, New York (Roberts).

Presented at the meeting of the American Laryngological Association, San Francisco, April 1-2, 1989.

REPRINTS — Pierre Lavertu, MD, Dept of Otolaryngology and Communicative Disorders, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195-5034.

TABLE 1. SUMMARY OF SURGICAL PROCEDURES

Caldwell-Luc	9
Partial maxillectomy	11
Total maxillectomy	2
Total maxillectomy, orbital exenteration	7
Anterior craniofacial resection	8
Anterior craniofacial resection, orbital exenteration	3
Total	40

TABLE 2. RECURRENCE BY SITE

Site	*No. of Patients (N = 29)*
Local	15
Distant	3
Local and regional	4
Local and distant	6
Local, regional, and distant	1

whole group and for various subgroups of the population.[5] The logrank test was used to test for differences in survival distributions.[6]

RESULTS

The 49 patients with nonsquamous cell malignancies ranged from 9 to 91 years of age (mean, 56 years). Twenty-five patients were female; 24 were male. Forty-four patients were white, 4 were black, and 1 was Hispanic. Thirty-nine patients had disease originating in the maxillary sinus, while 10 had ethmoid sinus primary tumors. There was no history of industrial exposure among any of the patients. Forty-four patients had computed tomography studies, 4 polytomography, and 1 plain film radiography.

By histologic type, 12 (25%) had a sarcoma; 10 (20%), adenoid cystic carcinoma; 9 (18%), lymphoma; 9 (18%), adenocarcinoma; and 9 (18%), other tumor types. The T stage was as follows: 1 patient, T1; 9 patients, T2; 16 patients, T3; and 23 patients, T4. Forty-six patients had N0 neck tumors, 1 presented with N2a, and 2 had N3a. There were no N1 neck tumors. Of the 3 patients with nodal disease, 1 had a T3 primary tumor and 2 had T4 primary tumors. Two patients presented with evidence of distant disease; both had T4 primary tumors. There was no trend of regional or distant metastases among the different histologic types.

Among the patients with sarcoma, the following histologic types were identified: fibrosarcoma (5), osteogenic sarcoma (2), rhabdomyosarcoma (2), malignant mesenchymoma (1), chondrosarcoma (1), and leiomyosarcoma (1). The lymphomas included histiocytic, large-cell lymphoma (8) and small, B-cell lymphoma (1). The adenocarcinomas included well-differentiated (3), moderately differentiated (3), and poorly differentiated (3) subtypes. Among the adenocarcinomas, two patients were noted to have a mucinous component and one had a papillary component. In the miscellaneous category, histologic types included malignant melanoma (3), mucoepidermoid carcinoma (3), plasmacytoma (2), and neuroblastoma (1). Two of the melanomas were melanotic and one was amelanotic. Two of the mucoepidermoid carcinomas were high-grade and one was low-grade.

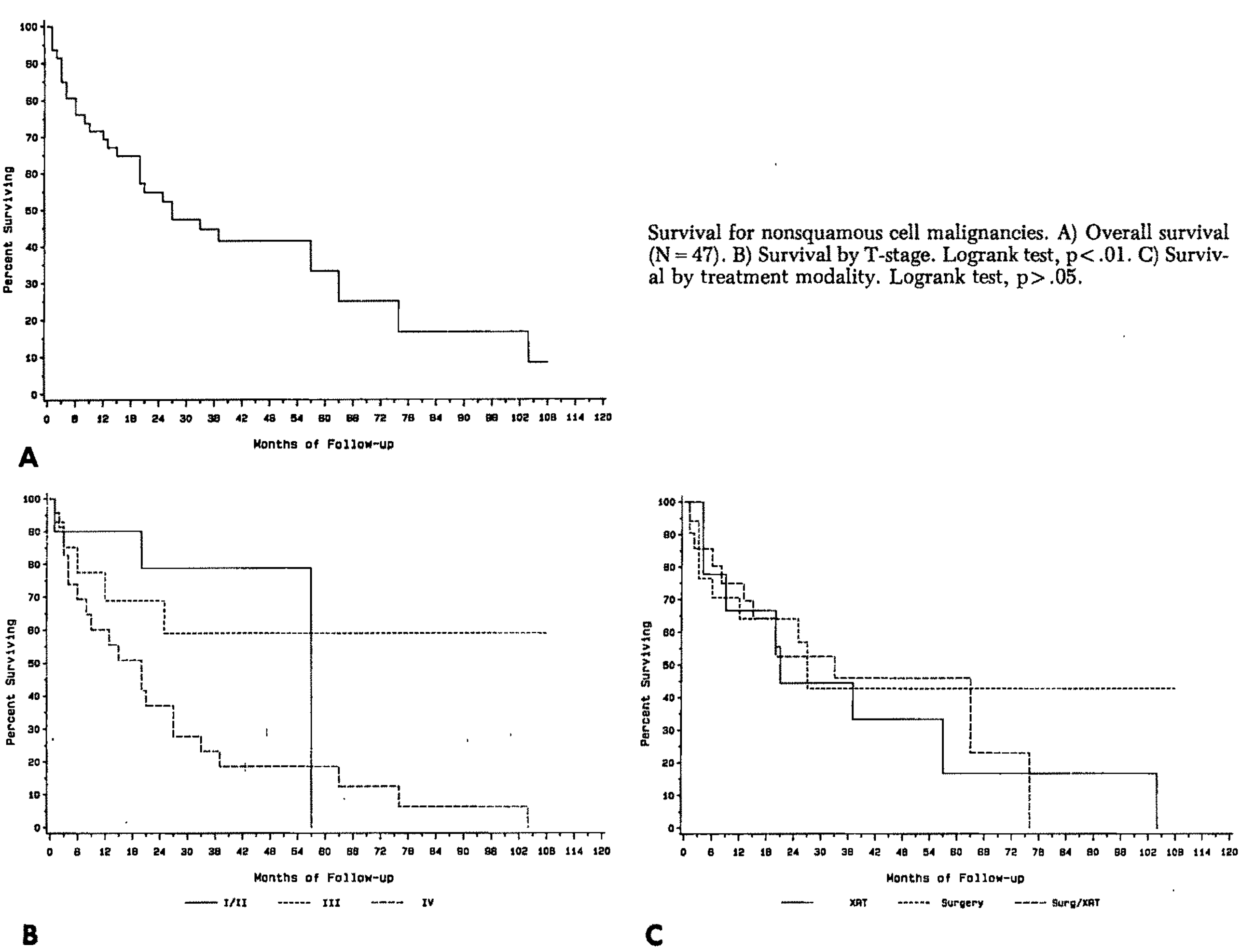
Treatment modalities were divided into three groups: 9 patients had radiation therapy alone, 17 had surgical treatment alone, and 23 had surgical treatment and postoperative radiation therapy. A summary of operations performed is given in Table 1, excluding the 9 patients with lymphoma who were treated with radiation therapy and/or chemotherapy after a surgical biopsy. The average radiation dose for both the radiation therapy alone and the postoperative radiation therapy was 5,700 cGy. Thirteen patients received chemotherapy in addition to their primary treatment. Four of these patients received palliative chemotherapy. The remainder were treated with curative intent; five of these patients had lymphoma.

Two patients, one with adenoid cystic carcinoma and one with lymphoma, were lost to long-term follow-up. Twenty-nine of the remaining 47 patients had recurrences at one or more sites. Twenty-six patients suffered at least one local recurrence. These recurrences occurred 1 month to 16 years after initial treatment. All except four recurrences occurred within 18 months. Two patients, one each with adenoid cystic carcinoma and fibrosarcoma, were entered into this study with local recurrence 16 years after initial management. Five patients developed regional metastases 1 to 12 months after therapy. Ten patients developed distant metastases 1 to 34 months after treatment. Several patients had recurrences at more than one site (Table 2). Among the 15 patients to present with or develop regional and/or distant metastases, 13 were dead of disease and 2 were alive with disease at the time of last follow-up.

Salvage therapy was attempted in 17 patients. Three patients, one each with fibrosarcoma, adenoid cystic carcinoma, and adenocarcinoma, had surgical salvage procedures. They have no evidence of disease at 49, 16, and 10 months, respectively. Three patients were alive with disease after attempted salvage; the remainder were dead with disease.

At the conclusion of this study, 15 patients were alive with no evidence of disease a median of 27 months following completion of the most recent treatment. Three of these patients were salvaged as noted. Six patients died with no evidence of disease, two of whom died in the immediate postoperative period. Three patients were alive with persistent disease. Twenty-three patients were dead of disease.

Statistical analysis revealed certain trends in sur-



Survival for nonsquamous cell malignancies. A) Overall survival (N = 47). B) Survival by T-stage. Logrank test, p < .01. C) Survival by treatment modality. Logrank test, p > .05.

vival distributions. Overall survival at 2 years was 55% and at 5 years was 33% (see Figure, A). Survival by T stage was significant (logrank test, p < .01), with improved survival in less extensive tumors (see Figure, B). Among the 10 patients with ethmoid sinus primary tumors, 2 were alive without disease, 2 were dead with no evidence of disease, 1 was alive with disease, and 5 were dead of disease. No significant difference was noted for survival by histologic type (Table 3). Among the patients alive with no evidence of disease were those with adenoid cystic carcinoma (4), histiocytic, large-cell lymphoma (4), fibrosarcoma (2), leiomyosarcoma (1), moderately differentiated adenocarcinoma (1), poorly differentiated adenocarcinoma (1), melanotic malignant melanoma (1), and plasmacytoma (1). The four long-term survivors who died with no evidence of disease had well-differentiated adenocarcinoma (2), amelanotic malignant melanoma (1), and histiocytic, large-cell lymphoma (1).

Survival analysis by treatment group revealed no statistically significant differences (see Figure, C). Among the nine patients to receive chemotherapy with curative intent, only three, treated for lymphoma, exhibited long-term survival. In patients undergoing surgical treatment, the report of surgical margins was available in 27 patients. Patients with negative margins may have a better survival experience, but this result was not significant (Table 4).

Of six patients who suffered complications related to treatment, two died. One patient died of cardiac arrest 3 weeks after operation. One patient had an intracranial abscess that was drained 1 month after operation; the patient died of a pulmonary embolism 2 months later. One patient developed osteomyelitis of the frontal bone, a cerebrospinal fluid leak, and meningitis; the bone flap was surgically debrided, and the patient recovered after long-term intravenous antibiotic therapy. One patient developed trismus due to resection of the pterygoid muscles requiring bilateral condylectomy, panhypopituitarism requiring hormone replacement, and a postoperative seizure disorder requiring antiseizure medication. The patient's symptoms were controlled for 5 years, followed by death from intracranial recurrence. One patient developed a cerebrospinal fluid leak associated with persistent disease at the skull base. The leak ceased after conservative therapy and the patient died of intracranial extension 11 months later. One patient developed a cataract in the eye adjacent to the radiation

TABLE 3. SURVIVAL STATUS BY TUMOR HISTOLOGY

Tumor	*NED*	*DNED*	*AWD*	*DWD*
Sarcoma	3	0	1	8
Adenoid cystic carcinoma	4	0	0	5
Adenocarcinoma	2	4*	0	3
Lymphoma	4	1	0	3
Miscellaneous	2	1	2	4
Total	15	6	3	23

Logrank test, $p > .05$. Two patients were lost to follow-up.

NED — no evidence of disease, DNED — died, no evidence of disease, AWD — alive with disease, DWD — dead with disease.

*Postoperative deaths = 2.

port; the patient declined further therapy because of an absence of functional disability.

DISCUSSION

Malignancies of the paranasal sinuses are associated with a generally poor prognosis. In a recent review a mean 5-year survival rate of 35% was noted.[7] Sisson et al[3] reported a 5-year survival rate of 49% for all patients with paranasal sinus malignancies. The most important predictor of treatment outcome is the T stage of the primary lesion, with less extensive lesions having a better prognosis. However, a majority of sinus malignancies present with an advanced T stage.[8] Early symptoms of sinus malignancy are nonspecific and overlap with those of infectious sinus disease. Symptoms associated with advanced local disease due to extension into the oral cavity, cheek, orbit, or cranial cavity are associated with a poor prognosis.

Early diagnosis and aggressive therapy are the cornerstone of successful treatment of paranasal sinus malignancies. Thorough history and physical examination, including nasal endoscopy, facilitate the early detection of these lesions. Radiographic assessment is imperative in individuals suspected of having a paranasal sinus malignancy. Computed tomography, in either the coronal or axial plane, will reveal destruction of the sinus walls with mass invasion into adjacent structures.[9] Magnetic resonance imaging may further define the degree of invasion, specifically into the anterior cranial fossa and orbit. Magnetic resonance imaging also differentiates between obstruction of a sinus ostium with collection of fluid versus tumor filling the entire sinus. When possible, intranasal endoscopy-guided biopsy or canine fossa puncture negates the need for a Caldwell-Luc maxillotomy, thus decreasing the theoretic risk of tumor seeding.[3]

Squamous cell carcinoma is the most common malignancy of the paranasal sinuses. Management is most successful with a combination of surgery and radiation therapy.[10] Seromucinous glands found in the sinus epithelium give rise to the less common adenocarcinoma and adenoid cystic, mucoepidermoid, and acinic cell carcinomas.[2]

Adenocarcinoma of the paranasal sinuses, in particular of the ethmoid sinus, has been linked to wood dust exposure. The trapping of biologically active compounds in the anterior ethmoid air cells with normal nasal respiration may be responsible for this association.[11] Several histologic conventions have been described. Well-, moderately, and poorly differentiated nonsalivary sinonasal adenocarcinomas are defined by differentiation of glandular elements and degree of local invasion. A distinct intestinal-type adenocarcinoma variant behaved similarly to the less aggressive well- and moderately differentiated adenocarcinomas.[12] Batsakis et al[13] distinguish between papillary, sessile, and alveolar adenocarcinoma subtypes. Papillary variants tend to be well localized; sessile and alveolar-mucoid variants are extremely invasive. The alveolar-mucoid type has abundant mucin production.[13] A resemblance to gastrointestinal tract adenocarcinoma is present in each of these variants.[14] Barnes[15] classifies intestinal-type adenocarcinoma into five categories: papillary, colonic, solid, mucinous, and mixed. Heffner et al[16] distinguish between low-grade and high-grade lesions on the basis of glandular pattern, nuclear pleomorphism, and mitotic rate. Prognosis was improved in the low-grade category. A similar classification was utilized by Goepfert et al[17]; low-grade adenocarcinoma exhibited pushing tumor margins, in contrast to infiltrative high-grade tumors. Local extent of tumor invasion and negative surgical margins are the best predictors of treatment outcome. Radiation plays an important adjuvant role, although in rare instances it has been the sole source of successful treatment.[17] The nine patients with adenocarcinoma in this series exhibited a broad spectrum of tumor differentiation; however, survival was not a function of tumor grade.

TABLE 4. SURVIVAL BY SURGICAL MARGINS

	NED	*DNED*	*AWD*	*DWD*	*Total*
Positive margins	1	1	3	7	12
Negative margins	8	2*	1	4	15

Logrank test, $p > .05$.

Abbreviations — see Table 3.

*Postoperative deaths = 2.

Two distinct histologic grading systems have been described for adenoid cystic carcinoma. Both systems are based on degree of tumor differentiation. Spiro et al[18] describe grade 1, cribriform pattern; grade 2, cribriform pattern mixed with basaloid or anaplastic features; and grade 3, predominant basaloid or anaplastic pattern. Goepfert et al[17] classify low-grade tumors as composed of a mixture of tubular and cribriform structures with solid anaplastic areas less than 30% of the neoplasm. High-grade tumors occurred with more than a 30% solid, anaplastic area.

In antral adenoid cystic carcinoma, the following patterns were noted: high incidence of local recurrence and distant metastases; rare cervical metastases; and a 7% 10-year survival. A nonsignificant trend was noted for improved survival with low-grade tumors.[18] The most valuable predictor of long-term survival was extent of the primary tumor with degree of local bone and soft tissue invasion. Surgery is the primary mode of therapy, with radiation reserved for unresectable, recurrent disease.[18] Goepfert et al[17] describe improved survival in low-grade adenoid cystic carcinoma. A higher incidence of local fulminant disease and distant metastases was noted in the high-grade pattern. Local recurrence of all grades resulted from perineural invasion and intracranial spread. Planned combined therapy offers the best 2-year local control, although survival was not different with surgical treatment alone. Long-term survival is difficult to assess because of the propensity for delayed distant metastases.[17] Of the five patients with treatment failure due to adenoid cystic carcinoma in this series, all five experienced local recurrence and three had distant metastases.

Mucoepidermoid carcinoma is the third most common salivary gland malignancy found in the minor salivary glands. Its occurrence in the paranasal sinuses is so rare that no representative reports exist. Histologic types are divided into low-grade, middle-grade, and high-grade classes based on mucus and cyst formation, cellularity, and histologic differentiation.[19] The three patients with mucoepidermoid carcinoma in this series failed treatment: two had local recurrence and one had distant metastases without primary-site recurrence.

Nonepithelial malignancies arising from the paranasal sinuses consist predominantly of sarcomas and lymphomas. In a review of 100 malignant nonepithelial tumors involving the nasal cavity, paranasal sinuses, and nasopharynx, 63 were sarcomas and 21 lymphomas.[20] The sarcomas included fibrosarcoma (19), rhabdomyosarcoma (16), osteogenic sarcoma (11), chondrosarcoma (10), leiomyosarcoma (6), and liposarcoma (1). Primary therapy generally consists of radical, en bloc surgical resection; most sarcomas are radioresistant. Recurrence patterns show frequent local recurrences and distant metastases.

Fibrosarcomas have been divided into two subtypes.[21] Fibromatosis, or well-differentiated fibrosarcoma, does not metastasize; however, local recurrence may result in treatment failure. Fibrosarcoma, the second subtype, is less likely to develop distant metastases in comparison to other sarcomas. This tumor grows at an extremely slow rate, has less local infiltration, and frequently is associated with negative surgical margins. Large en bloc resections are recommended; radiation therapy does not play a role. Two of five patients with fibrosarcoma in this series, one of whom had recurrence 16 years after initial management, were successfully treated. The three patients who were treatment failures had recurrence at the primary site, and two of these patients had metastatic disease.

Rhabdomyosarcoma in this area typically occurs in children. One patient in this series was an adult. Unlike orbital rhabdomyosarcoma, tumors at this site are associated with dismal long-term survival.[22] Radical surgical resection is often not feasible because of size, location, and involvement of local structures. Adjuvant chemotherapy and radiation therapy have been associated with improved survival in the head and neck. Recurrences occur locally and distantly, with occasional regional lymph node involvement noted. The two patients in this series with rhabdomyosarcoma failed treatment because of disseminated disease.

Many patients with osteogenic sarcoma have received radiation therapy for unrelated disease. In a group of four patients, the sarcoma developed an average of 16 years after radiation therapy.[23] The two patients in this series had no prior radiation exposure. Treatment failure is typically due to local recurrence. Five-year survival varies from 9% to 23%.[20,21] An association between Paget's disease, fibrous dysplasia, and osteogenic sarcoma has been described. Radical surgical resection is the treatment of choice.[24] Treatment failure in the two patients with osteogenic sarcoma in this series was due to local recurrence.

Chondrosarcomas tend to be locally advanced at the time of diagnosis.[25] En bloc resection is associated with a 50% 5-year survival. An improved prognosis is noted in patients with low-grade tumors and negative surgical margins. Malignant mesenchymoma is considered a distinct subset of chondrosarcoma by some authors and a poorly differentiated variant by others.[25,26] This tumor arises from primitive mesenchymal cells with the potential to differentiate into cartilage. Tumors arise from both skeletal and soft tissues. Histologic confusion with hemangiopericytoma occurs because of the proliferation of tumor cells adjacent to vascular channels.[26] Optimal therapy requires radical surgical excision. Optimism concerning long-term survival must be tempered by the occurrence of delayed hematogenous metastases to the lungs. Two patients in this series, one each with chondrosarcoma and malignant mesenchymoma, failed treatment because of local recurrence.

Leiomyosarcomas are a rare entity in this region, with an extremely poor prognosis.[27] Therapy is primarily surgical. Treatment failure has been associated with incomplete excision, local recurrence, and pulmonary metastases. The one patient in this series with leiomyosarcoma has no evidence of recurrent disease.

In a review of patients at the Massachusetts Eye and Ear Infirmary, 8% of sinus cancers were lymphomas. All patients had non-Hodgkin's lymphoma (reticulum cell sarcoma).[28] Radiation therapy was the primary mode of treatment, with a 26% 5-year survival. In another series of 17 patients, there were 9 with reticulum cell sarcoma, 5 with poorly differentiated lymphocytic tumors, and 3 with mixed histiocytic-lymphocytic lymphoma.[29] Treatment was primarily radiation therapy, with improved survival in the patients with poorly differentiated lymphoma. A poor prognosis was associated with a poor clinical response to radiation therapy and the development of disseminated lymphoma during treatment. Long-term survival at the conclusion of the study was 29%. In 17 patients reviewed by Fu and Perzin,[30] 12 had a reticulum cell sarcoma; 3, moderately differentiated lymphoblastic lymphoma; and 2, well-differentiated lymphocytic lymphoma. Long-term survival was obtained in only 13%. Primary therapy was irradiation, and treatment failures were due to distant disease. The role of adjuvant chemotherapy in preventing or controlling disseminated disease must be considered in this patient population. Five of eight patients in this series with lymphoma had long-term survival. Among the three treatment failures, two had systemic disease on presentation. One patient died with disease limited to the primary site.

Malignant melanoma in the paranasal sinuses arises from mucosal and submucosal melanocytes, of which only two thirds are melanin-producing.[2] The maxillary sinus is most frequently involved, there is limited local extension, and rarely are cervical or distant metastases evident on initial presentation. Patients undergoing radical local excision with postoperative radiation therapy remain at risk for developing local recurrence and delayed distant metastases. Five-year survival ranges from 30% to 38%.[2,31] One of three patients with malignant melanoma in this series failed therapy; recurrence occurred at the primary site. Primary extramedullary plasmacytoma occurs rarely in the paranasal sinuses; this is consistent with the two patients in this series. Treatment includes surgical debridement and postoperative radiation therapy. The 5-year survival in 24 patients was 53%.[32] Disseminated disease in the form of multiple myeloma was the only cause of mortality; local recurrence did not result in death. In a separate report, one death was credited to local persistent disease.[33]

Discussion of surgical management is beyond the scope of this article. The orbit may be spared when the globe is not grossly involved and the patient receives radiation therapy prior to definitive resection.[3] No difference in survival has been noted when the periorbita does not contain viable tumor cells.[3] The 19% of patients who underwent orbital exenteration in this series had massive orbital involvement and were not candidates for globe-sparing procedures. Craniofacial resection has extended the limit of surgical resectability, often providing negative surgical margins. The importance of negative surgical margins is evident in this study: 10 of 12 patients with positive margins were treatment failures and 8 of 13 patients with negative margins had long-term survival.

CONCLUSION

Nonsquamous cell malignancies of the paranasal sinuses are a heterogeneous group of tumors with an overall poor prognosis. Treatment depends on tumor histology and degree of local invasion. Radical en bloc resection is recommended for sarcoma, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, and malignant melanoma. A majority of sarcomas are radioresistant; the remaining tumors may benefit from combination therapy. Treatment failure is primarily due to local recurrence and frequently due to distant metastases. Lymphoma and plasmacytoma are treated with radiation therapy; chemotherapy may play an adjuvant role. Treatment failure generally occurs with the development of disseminated disease. The most important prognostic factor for survival in nonsquamous cell malignancies appears to be the degree of local invasion at presentation. Survival estimates are similar for the different histologic types. The sporadic occurrence of these tumors mandates multi-institutional, prospective studies to determine optimal treatment.

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SUPRAGLOTTIC CARCINOMA: PATTERNS OF RECURRENCE

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A retrospective review of 202 patients with supraglottic squamous cell carcinoma and at least 2 years of follow-up was performed. Surgery alone was used to treat 102 patients, and combined therapy in 100 patients. Local-regional failure occurred in 47 (23%) patients. Only 4 patients (2%) developed recurrence at the primary site. The neck was the most common site for recurrent disease (39/47 or 83%), which in 35 patients appeared in the undissected, contralateral side. The risk to the contralateral side of the neck in patients with midline (epiglottic) lesions was similar to that in those with unilateral (aryepiglottic fold) lesions. Supraglottic laryngectomy, when properly selected, did not compromise primary control in the larynx. Radiation therapy was ineffective in controlling metastasis to the contralateral side of the neck in 16 of 99 patients (16%). Therefore, routine bilateral neck dissection should be considered in the surgical treatment of supraglottic carcinoma for control of regional disease.

KEY WORDS — recurrence, supraglottic squamous cell carcinoma.

INTRODUCTION

The optimal management of cancer of the supraglottic larynx remains unsettled. Although adequate control of even extensive primary cancers can be achieved surgically, the control of metastases to the cervical region, the most common site of failure, is less certain.

Elegant anatomic and embryologic studies by Pressman et al,[1] Tucker,[2] Oloffson,[3] and Kirchner and Som[4] have produced important information. Lesions can easily involve the preepiglottic space by direct invasion along mucous glands within the multiple fenestrations of the epiglottic cartilage and can result in bilateral lymphatic tumor dissemination. The supraglottic site most commonly involved by tumor is the epiglottis, followed by the false cord, aryepiglottic fold, and ventricle. Approximately 70% of all epiglottic and 50% of all supraglottic lesions have been found to involve the preepiglottic space.[5,6]

Tumor location may have prognostic significance. Lesions of the marginal zone, or "epilarynx," including the posterior part of the aryepiglottic fold and the suprahyoid margin of the epiglottis, reportedly behave more aggressively, similarly to hypopharyngeal lesions, with an increased incidence of cervical metastases.[7,8]

The compartments of the larynx and barriers to early tumor spread have been well defined.[9,10] Unlike the glottis, which is formed by the fusion of two lateral cell masses in the midline at the anterior commissure, the supraglottis has no well-defined fusion plane. Central epiglottic and anterior false cord lesions can easily spread across the midline in the so-called horseshoe pattern. Spread to the paraglottic space and glottis may occur in more advanced lesions. The feasibility of primary tumor control by supraglottic laryngectomy has been well documented in carefully assessed patients.

In order to further evaluate our management of supraglottic cancer, a retrospective review was performed. Several issues were to be considered, including the possible prognostic importance of midline (epiglottic) versus lateral (aryepiglottic fold) tumor location, the site(s) of failure, and the effectiveness of treatment modalities on local-regional control.

MATERIALS AND METHODS

A retrospective review of patients with squamous cell carcinoma of the supraglottic larynx diagnosed and treated with surgery from 1975 to 1986 was performed.

Tumor diagrams and pathology reports were employed to classify the tumors according to site and stage. The use of adjuvant therapy was assessed. Patient follow-up was documented, and the outcome of treatment recorded.

The lesions were classified as either epiglottic or aryepiglottic after review of pathology reports and tumor diagrams. Extrinsic tumors with extension outside the larynx to involve the tongue base or pyriform sinus were not included in this study. Epiglottic lesions included lesions of the epiglottis and "horseshoe" lesions of the false cords, including all lesions with bilateral involvement. Aryepiglottic fold lesions included unilateral lesions of the epilarynx, including the false vocal cord, aryepiglottic fold, and medial wall of the pyriform sinus.

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REPRINTS — Bruce Johnston, Medical Library, Eye and Ear Institute, 203 Lothrop St, Pittsburgh, PA 15213.

TABLE 1. SURVIVAL BY PRIMARY SITE FOR SUPRAGLOTTIC CARCINOMA

	Aryepiglottic Fold		*Epiglottis*		*Total*	
	No. of Pts	*%*	*No. of Pts*	*%*	*No. of Pts*	*%*
Stage I	0/ 0	0	2/ 3	67	2/ 3	67
Stage II	9/11	82	44/ 54	81	53/ 65	82
Stage III	17/21	81	32/ 37	86	49/ 58	84
Stage IV	21/36	58	21/ 40	53	42/ 76	55
Total	47/68	69	99/134	74	146/202	72

RESULTS

A group of 225 patients treated surgically with squamous cell carcinoma of the supraglottic larynx was identified. All were followed a minimum of 24 months or until death. Twenty-three patients died without cancer, of causes unrelated to the lesion, with less than a minimum follow-up of 24 months, and their outcome was deemed indeterminate. The remaining 202 patients are the subject of this paper.

The mean follow-up was 54 months. The male: female ratio was 2:1. Ages ranged from 36 to 83 years, with a mean age of 59 years. Surgery alone was used to treat 102 patients, and combined therapy was used in 100 patients. The majority of patients were treated with unilateral neck dissection. The decision to perform elective neck dissection in patients with no palpable metastasis was based upon the side of the larynx with the greatest amount of visible tumor. The subsequent decision to employ postoperative radiation therapy was based upon the pathology report and the surgeon's judgment of risk to the contralateral side of the neck.

Midline epiglottic lesions accounted for 134 (66%) of the cases, while lateral aryepiglottic fold lesions accounted for 68 cases (34%). Three lesions were classified as stage I, 65 were classified as stage II, 58 were classified as stage III, and 76 were classified as stage IV, according to the staging system recommended by the American Joint Committee (1980).[11]

The 2-year survival rates were 2 of 3 (67%), 53 of 65 (82%), 49 of 58 (84%), and 42 of 76 (55%) in stages I, II, III, and IV, respectively. The overall 2-year survival rate was 146 of 202 (72%).

Although the lesions had been separated according to location, no difference in survival by stage, primary tumor control, or pattern of recurrence was noted between midline epiglottic lesions and aryepiglottic fold lesions when data were controlled for stage of the primary lesion (Table 1). It should be noted, however, that the patients with aryepiglottic fold lesions presented with more advanced primary tumors than the patients with epiglottic lesions. Stage III and IV lesions were encountered in 57 of 68 (84%) of aryepiglottic fold patients, compared to 77 of 134 (57%) of the epiglottic patients ($p<.001$).

TABLE 2. NECK FAILURE RELATED TO NODAL STATUS AND TREATMENT MODALITY

	Radiotherapy + Surgery		*Surgery Alone*		*Total*	
	No. of Pts	*%*	*No. of Pts*	*%*	*No. of Pts*	*%*
N0	2/36	6	12/ 70	17	14/106	13
N1	1/14	7	5/ 20	25	6/ 34	18
N2	12/39	31	5/ 10	50	17/ 49	35
N3	2/10	20	0/ 2	0	2/ 12	17
Initial failure	17/99	17	22/102	22	39/201	19
Salvaged	2/17	12	10/ 22	45	12/ 39	31
Final failure	15/99	15	12/102	12	27/201	13

Local-regional failure occurred in 47 (23%) patients overall. The most common site for local-regional failure was the cervical lymphatics. Of the 47 patients with recurrent disease, 39 (87%) developed cervical metastasis. This included 3 patients who failed in the ipsilateral side of the neck, 35 patients who failed in the contralateral unoperated side of the neck, and 1 patient who failed in both sides of the neck. Only 2% of the entire group (4/202) had recurrences in the laryngopharynx. Four other patients had recurrences in unclassified sites in the head and neck (see below) and are counted as miscellaneous.

The contralateral (unoperated) side of the neck was the most common site of failure. This observation was similar in patients with lateral (aryepiglottic fold) lesions when compared to patients with midline (epiglottic) lesions. When unilateral neck dissection demonstrated histologically positive nodal metastasis in the ipsilateral side of the neck, the subsequent neck recurrence rate was 26% (25/95), compared to 13% (14/107) when no metastatic nodes were identified in the dissected neck. Similarly, histologic evidence of positive nodal status resulted in a poorer prognosis, with cure rates of 62% (59/95), compared to 81% (87/107) for patients with no evidence of cervical metastasis ($p<.05$).

Planned radiation therapy in conjunction with surgery was used in 99 patients. Radiation therapy ranged from 30 to 70 Gy in divided dosage, with a mean of 62 Gy. Therapy was directed at the primary tumor bed and the neck bilaterally.

Recurrence in the neck developed in 17% (17/99) of these patients (Table 2). This included recurrence in the undissected contralateral side of the neck in 16 patients (16%) in whom no palpable disease (N0) existed. In all 17 patients, control of the primary tumor was documented. Only 2 of these 17 patients were salvaged by subsequent therapy.

In comparison, recurrence in the cervical lymphatics developed in 22% (22/102) of patients treated by surgery alone (Table 2). This included 19 patients who had recurrences in the contralateral, and 1 in the ipsilateral, untreated side of the neck.

TABLE 3. SURVIVAL BY STAGE RELATED TO TREATMENT MODALITY

	Radiotherapy + Surgery		Surgery Alone	
	No. of Pts	*%*	*No. of Pts*	*%*
Stage I	0/ 1	0	2/ 2	100
Stage II	13/15	87	40/ 50	80
Stage III	21/25	81	28/ 32	88
Stage IV	33/58	57	9/ 18	50
Total	67/99	67	79/102	77

Ten of these patients were ultimately salvaged with further therapy.

Surgery of the supraglottic primary tumor consisted of either supraglottic or total laryngectomy, usually in conjunction with an ipsilateral or bilateral neck dissection. No neck dissection was performed in 16 patients, 158 patients underwent a unilateral neck dissection, and 28 patients were treated with bilateral neck dissections. Of the 214 neck dissections performed in 186 patients, only 3 of the operated sides of the neck were eventually the site of recurrent disease. In 2 of these 3 patients, bilateral neck dissection had been performed: 1 patient had bilateral positive neck nodes, and the other patient had bilateral negative nodes.

Supraglottic laryngectomy was performed in 72 patients, and total laryngectomy in 130 patients. Of the 72 supraglottic laryngectomy patients, primary failure occurred in 1 (1%), and neck failure occurred in 13 (18%). Following total laryngectomy, primary failure occurred in 3 of 130 patients (2%), and neck failure occurred in 26 of 130 patients (20%).

In the entire study population, recurrent disease occurred at the primary site in four patients, all of whom had epiglottic lesions. In each case, recurrence was at the base of the tongue. All four primary failures were in stage IV patients, three of whom received radiation therapy in combination with surgery. Four head and neck recurrences were classified as miscellaneous. This included two stomal recurrences, one base of skull recurrence, and one cutaneous implant. Of the 47 patients with local-regional failure, 34 patients (72%) eventually died of their carcinoma.

Distant metastases occurred as the sole cause of failure in 22 of 202 (11%) patients. The sites of distant metastasis were lung in 17 patients, bone and liver in 3 patients each, and subclavian soft tissue, unrelated to neck disease, in 1. In the surgery and irradiation group, 14 of 99 patients (14%) had distant metastasis. The surgery-alone group had 9 of 102 patients (9%) with distant metastasis. Five of these 9 patients had no evidence of cervical metastasis. Of the entire group of 23 patients with distant metastasis, 10 (43%) had documented extracapsular spread of tumor.

Surgery alone was used to treat 102 patients, with 2-year survival rates for stages I, II, III, and IV of 2 of 2 (100%), 40 of 50 (80%), 28 of 32 (88%), and 9 of 18 (50%), respectively, for an overall survival rate of 79 of 102 (77%) (Table 3). Combined therapy consisting of planned preoperative or postoperative irradiation and surgery resulted in 2-year survival rates for stages I, II, III, and IV of 0 of 1 (0%), 13 of 15 (87%), 21 of 25 (81%), and 33 of 58 (57%), respectively, for an overall survival rate of 67 of 99 (67%) (Table 3). One patient received surgery and chemotherapy and is excluded from discussion of either surgery alone or irradiation and surgery comparisons. There was not a statistically significant difference in outcome when surgery alone was compared to combined therapy ($p > .05$). However, this uncontrolled retrospective study does not allow direct comparison of the two groups.

TABLE 4. TWO-YEAR SURVIVAL RATES RELATED TO NODAL STATUS AND TREATMENT MODALITY

	Radiotherapy + Surgery		Surgery Alone	
	No. of Pts	*%*	*No. of Pts*	*%*
N0	30/36	83	56/ 70	80
N1	11/14	79	18/ 20	90
N2	22/39	56	3/ 10	30
N3	3/10	30	2/ 2	100
Total	66/99	66	79/102	77

Of the 202 patients, 118 (58%) are alive without evidence of disease, 28 (14%) patients died of other causes with a minimum follow-up of 24 months and demonstrated no evidence of recurrent or metastatic disease, and 56 (28%) patients are dead of disease. Recurrence was noted at a mean of 16.7 months, with 85% of all recurrent disease noted within the first 2½ years after initial treatment.

CONCLUSION

Attempts to attribute prognostic significance to primary tumor location have been proposed.[7,8,12] Although our initial assumption was that lateral lesions may behave differently than midline lesions, especially in patterns of cervical recurrence, the data demonstrate no differences (Table 1). In particular, the risk for contralateral cervical metastasis is similar for lateral (aryepiglottic fold) lesions and midline (epiglottic) lesions.

Primary tumor control was excellent, with only 4 failures at the primary site in 202 patients (2%). A survey of the literature suggests that radiation therapy fails to control the primary tumor in approximately 30% of cases.[13-15] Therefore, surgery seems to offer more consistent control of the primary tumor.

The overall survival, by stage, was not statistically altered in combined therapy compared to surgery alone (Table 3). Similarly, the data in Table 4 reflect no improvement in survival rates in patients treated with combined therapy or surgery alone

TABLE 5. NECK FAILURE AND SURVIVAL FOR T STAGE AND NODAL STATUS

	Neck Failure		*Survival**	
	No. of Pts	*%*	*No. of Pts*	*%*
T1	0/ 3	0	2/ 3	67
T2	20/108	19	82/108	76
T3	8/ 55	15	44/ 55	80
T4	10/ 35	29	18/ 35	51
Tx	1/ 1	100	0/ 1	0
N0†	14/107	13	87/107	81
N1†	6/ 34	18	29/ 34	85
N2†	17/ 49	35	25/ 49	50
N3†	2/ 12	17	5/ 12	42
Total	39/202	19	146/202	72

*Reflects outcome after salvage of recurrent disease.

†Reflects pathologic staging.

when nodal status is considered. These data, however, reflect a great deal of treatment selection and should not be considered comparative.

Although the numbers were small, no difference existed in the 2-year survival for preoperative compared to postoperative radiation therapy: 18 of 27 (67%) and 48 of 72 (67%), respectively.

Supraglottic laryngectomy has been widely accepted as an oncologically sound procedure.[16-22] When carefully selected, supraglottic laryngectomy did not result in any difference in achieving primary control compared to total laryngectomy. As previously noted in the literature,[23] tumor margins in the base of the tongue remain the most difficult to eradicate, especially with advanced epiglottic lesions. The difficulty with achieving a proper margin at the tongue base is similar with either total laryngectomy or supraglottic laryngectomy.

Supraglottic laryngectomy was offered when, in the surgeon's judgment, the tumor could be removed with clear margins and the patient had enough cardiopulmonary reserve to tolerate temporary aspiration. The most common forms of tumor involvement to rule out conservation laryngeal surgery were paraglottic extension, involvement of the arytenoid, and extension from the petiole to the anterior commissure. Only in exceptional cases was unilateral arytenoidectomy combined with supraglottic laryngectomy.

No set guidelines for pulmonary function have been established to help determine feasibility of supraglottic laryngectomy; however, we require that a patient be able to climb two flights of stairs unaided and give evidence of an active life-style. Any impairment to ambulation (eg, amputation) is considered an absolute contraindication to supraglottic laryngectomy in our institution.

The extent of the primary did not alter the rate of regional recurrence or survival, except for T4 lesions (Table 5). Nodal disease, as previously reported, was a much more important measure of prognosis.[24,25] Patients with histologically negative nodes had a 2-year survival of 81% (87/107). Positive nodal status was associated with a 2-year survival rate of 62% (59/95). Further evaluation of nodal status (Table 5) reveals that pathologic N0 disease and N1 disease were similar in neck failure (13% and 18%, respectively) and 2-year survival (81% and 85%, respectively). However, N2 and N3 nodal status was associated with an increased rate of neck failure of 19 of 61 (31%) and decreased 2-year survival rate of 30 of 61 (49%), when compared to N0 and N1 nodal disease ($p<.01$). Extracapsular spread was associated with an increased neck failure rate of 27 of 44 (27%), a distant metastatic rate of 10 of 44 (23%), and a 2-year survival rate of 22 of 44 (50%).

If surgery is so successful in achieving primary control, where then do we fail in controlling carcinoma of the supraglottic larynx? The largest site of regional failure remains the neck. Regional failure occurred in 43 of 202 (21%) patients, with 2 failures at the stoma, 1 at the base of the skull, 1 of the skin, and 39 in the cervical lymphatics. These 39 patients failed in the neck despite control of the primary tumor. Salvage of neck failures was successful in 12 patients (31%). Twenty-seven patients (69%) died of disease. Interestingly, the salvage rate was lessened in patients who received radiation therapy. Of the patients receiving radiation therapy in combination with surgery, only 2 of 17 (12%) were successfully salvaged, while in the surgery group, 10 of 22 (45%) were successfully salvaged. At first glance, initial failure rates seemed to be slightly lower with surgery and irradiation (17/99 or 17%) than with surgery alone (22/102 or 22%). However, once the salvage rates were considered, the overall neck failure rates decreased to 15 of 99 (15%) in the surgery-plus-irradiation group and 12 of 102 (12%) in the surgery-alone group, or 27 of 201 (13%) overall (Table 2).

Sixteen patients were treated with either supraglottic or total laryngectomy without neck dissections. Nine patients had only surgery, and seven patients had adjuvant radiation therapy. The numbers are small, but one patient failed in each group and only the patient without irradiation was salvaged.

In our series of 202 patients, 16 patients had no neck dissections, 28 had bilateral neck dissections, and 158 underwent unilateral neck dissection. Only 3 (1%) of the 214 neck dissections in 186 patients resulted in recurrence on an operated side. The remaining 36 neck failures occurred in an unoperated side, 35 of which were in the unoperated side deemed contralateral to the primary lesion. Seventeen (44%) of the 39 neck failures occurred in patients who had received radiation therapy; 16 of the 17 failed in the unoperated N0 side. The failure of irradiation to prevent regional recurrence in 16 of 99 (16%) clinically N0 sides of the neck was trou-

TABLE 6. NECK FAILURE AND SURVIVAL WITH AND WITHOUT BILATERAL NECK DISSECTION

	With		*Without*	
	No. of Pts	*%*	*No. of Pts*	*%*
Neck failure				
N0 + N1	1/16	6	19/125	15
N2 + N3	1/12	8	18/ 49	37
Total	2/28	7	37/174	21
Survival				
N0 + N1	14/16	88	102/125	82
N2 + N3	7/12	58	23/ 49	46
Total	21/28	75	125/174	72

blesome.

Of the 214 neck dissections, 108 (50%) were histologically positive for metastatic disease. Of the 190 N0 sides of the neck that were managed without surgery, 36 were in patients who failed. Therefore, 144 of 404 (36%) sides of the neck eventually manifested cervical metastasis in 131 (65%) patients.

Of the 28 patients with bilateral neck dissections (Table 6), only 2 patients (7%) failed in the neck. In patients treated without bilateral neck dissections, cervical recurrence in the unoperated side of the neck occurred in 36 of 174 (21%) patients. The numbers are small and do not achieve significant difference ($p > .05$). Survival data were similar in patients treated with or without bilateral neck dissections. Patients selected for bilateral neck dissections were judged by the surgeon to be at greatest risk for bilateral cervical metastasis. Despite this selection bias, a trend to lower rates of neck recurrence was apparent.

Our data support the assertions of Bocca et al[26] concerning the need for bilateral neck dissection in supraglottic carcinoma. Other authors have demonstrated the propensity for failure in the contralateral untreated sides of the neck in supraglottic carcinoma, accounting for 78%[23] and 75%[24] of neck failures. Poor survival after neck recurrence is also well documented, with mortality of 69% in our study. The high risk of metastasis to the contralateral cervical lymphatics independent of the site of the primary tumor and the poor survival associated with neck recurrence argue convincingly for treatment of both sides of the neck at the time of excision of the primary lesion. The data presented seem to be a clear call for elective bilateral neck dissection for all patients treated surgically for carcinoma of the supraglottic larynx.

SUMMARY

1. Whether the primary supraglottic tumor was in the lateral (aryepiglottic fold) or midline (epiglottis) location did not alter survival or pattern of recurrence.
2. Supraglottic laryngectomy, in properly selected cases, offered equal control of primary disease compared to total laryngectomy. Surgical excision of the primary tumor offers superior control compared to reports of primary radiation therapy.
3. The neck, especially the contralateral unoperated side, remains the greatest site of failure.
4. Positive nodal status, especially pathologic N2 and N3, was associated with greater regional recurrence and decreased survival.
5. Bilateral neck dissection is recommended for treating carcinoma of the supraglottic larynx.

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NINDS NOTES*

NINDS ANNOUNCES $750,000 CEILING ON GRANTS

The National Institute of Neurological Disorders and Stroke (NINDS) has announced a $750,000 ceiling on applications for program project and clinical research center grants. The ceiling is effective for the submission deadline of February 1, 1990.

Applications that request more than $750,000 in direct costs for any one of the five proposed years of support will be returned to the applicant without review. The new ceiling also applies to applications for supplements, which may not bring the total grant amount to more than $750,000 per year.

Competing continuation applications for program project and clinical research center grants currently awaiting review or award may be allowed more than $750,000 for the first year of continuation support, but in subsequent years will be reduced to the ceiling amount.

For additional information concerning the new guidelines, contact John C. Dalton, PhD, Division of Extramural Activities, NINDS, Federal Building, Room 1016, Bethesda, MD 20892; (301) 496-9248.

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RESEARCH CAREER DEVELOPMENT AWARDS

Application deadlines for Clinical Investigator Development Awards and Research Career Development Awards are February 1, June 1, and October 1 of each year.

Additional information can be obtained from Edward M. Donohue, Deputy Director, Division of Extramural Activities, NINDS, NIH, Bethesda, MD 20892; (301) 496-4188.

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*This information is prepared monthly by the Office of Scientific and Health Reports, NINDS, NIH, Bldg 31, Rm 8A-06, Bethesda, MD 20892; (301) 496-5924.

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ROLE OF THE SOFT PALATE IN LARYNGEAL FUNCTIONS AND SELECTED VOICE QUALITIES

SIMULTANEOUS VELOLARYNGEAL VIDEOENDOSCOPY

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The role of the soft palate in normal laryngeal functions and in the production of selected voice qualities was studied by a simultaneous velolaryngeal videoendoscopy technique. For this technique, the Olympus ENF-P flexible nasopharyngolaryngoscope was passed via one nostril to study the function of the larynx, while the Hopkins 70° rhinoscopic telescope was passed via the other nostril to study the function of the soft palate and velopharyngeal closure. A Kay Elemetrics DSP Sona-Graph, model 5500, was used to analyze a complex vocal figure of five consecutive voice qualities, three of which were nasal, and two, oral. Simultaneous velolaryngeal videoendoscopy proved to be of great value for the understanding of the interaction of velar and laryngeal functions and for clarifying the mechanisms of nasal and twang qualities.

KEY WORDS — laryngeal function, simultaneous velolaryngeal videoendoscopy, voice quality.

The soft palate (velum palatinum, palatum molle) is a fibromuscular shelf that projects backward and downward from the posterior edge of the hard palate. The nipple-like uvula, of variable length, projects downward from its posterior free edge in the midline. Laterally, the soft palate arches run downward in front of and behind the palatine tonsils, helping to bound the pharyngeal fauces.[1] It is generally believed that during quiet respiration, the soft palate is almost vertical, but during speech, its anterior two thirds is raised to the level of the hard palate, and only its more posterior part curves downward.

Many different methods have been used for documenting the soft palate in normal and in pathologic states. These methods include fiberscopic and telescopic endoscopy,[2-11] electromyography,[12,13] cephalometric x-ray studies,[14] cineradiography,[15,16] videofluorography,[9,17] computed tomography,[6] cine-computed tomography,[18] and magnetic resonance imaging.[19]

With the advent of the flexible nasopharyngolaryngoscope and the rigid rhinoscopic telescope, movements both above and below the soft palate are now accessible to view. However, both instruments present certain limitations. The flexible scope is limited by the difficulty in stabilizing the tip of the fiberscope due to the movement of the soft palate. The rigid scope has minimized the problem of stabilization, allowing the study of movement of anatomic structures unhindered by the artifacts imposed by movement of the endoscope. However, while recent studies indicate that the Hopkins 70° rigid telescope is one of the most useful instruments for the study of the function of the soft palate and velopharyngeal closure,[7,9,10] the 70° telescope is not always easy to insert, as the floor of the nasal cavity rather than the oncoming nasopharynx is in view during passage.[10]

Despite the problems inherent in both the flexible fiberscope and the 70° rigid telescope, each provides a particular advantage in viewing the function of the soft palate in relation to other parts of the vocal mechanism. The rigid telescope gives a clearer view of the soft palate and the velopharyngeal opening above, while the flexible fiberscope is better able to show the simultaneous changes occurring in the vocal apparatus below.

The purpose of this study is to examine the role of the soft palate in normal laryngeal functions, as well as in its contribution to nasal and oral voice qualities, by means of the simultaneous velolaryngeal endoscopy technique.

MATERIALS AND METHOD

Subjects. Sixteen volunteer subjects were studied: 6 men and 10 women. The ages ranged from 23 to 69, with a mean age of 37. Of these 16, 14 subjects tolerated simultaneous velolaryngeal endoscopy well, while 2 subjects could not (one because of marked septal deformity and hypertrophy of turbinates and the other because of extreme apprehension). While normal laryngeal functions were studied in 14 subjects, 8 were singers who performed additional tasks with nasal and non-nasal qualities.

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REPRINTS — Eiji Yanagisawa, MD, 98 York St, New Haven, CT 06511.

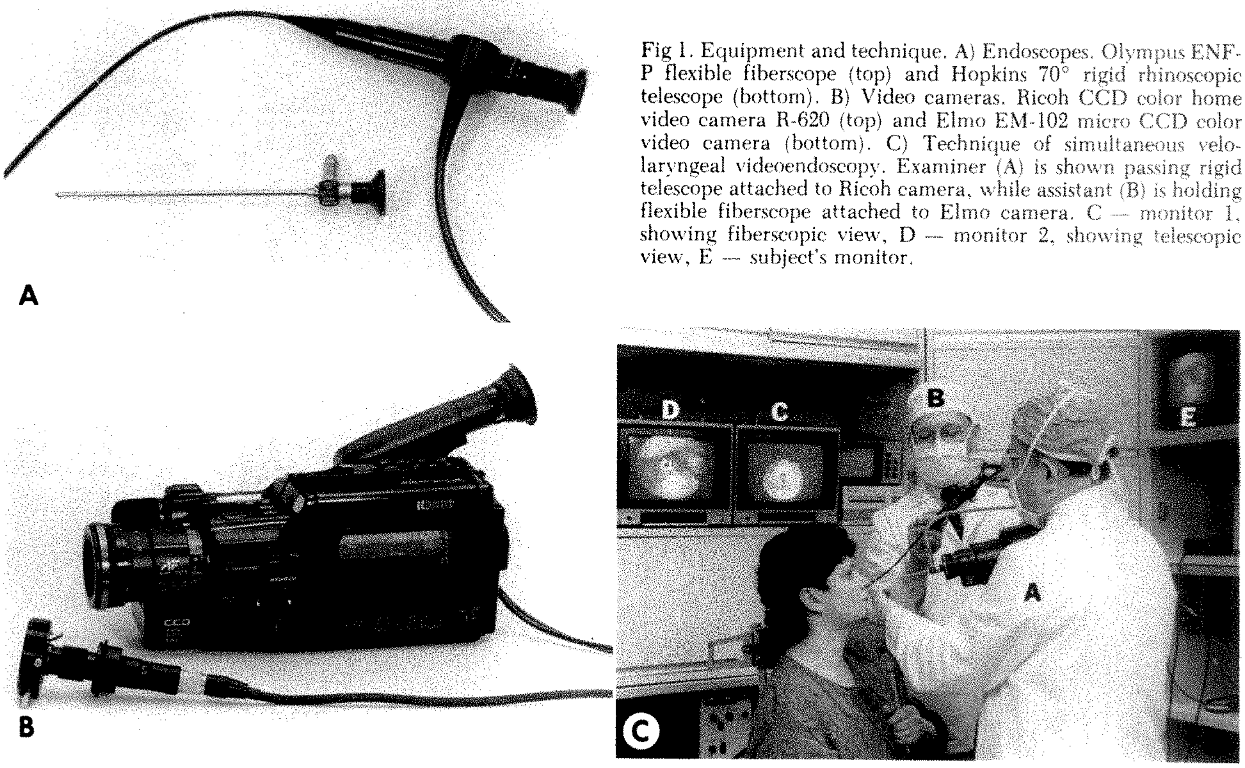

Fig 1. Equipment and technique. A) Endoscopes. Olympus ENF-P flexible fiberscope (top) and Hopkins 70° rigid rhinoscopic telescope (bottom). B) Video cameras. Ricoh CCD color home video camera R-620 (top) and Elmo EM-102 micro CCD color video camera (bottom). C) Technique of simultaneous velolaryngeal videoendoscopy. Examiner (A) is shown passing rigid telescope attached to Ricoh camera, while assistant (B) is holding flexible fiberscope attached to Elmo camera. C — monitor 1, showing fiberscopic view, D — monitor 2, showing telescopic view, E — subject's monitor.

Equipment. The following equipment was used for this study: 1) an Olympus ENF-P flexible rhinolaryngofiberscope (Fig 1A); 2) a Hopkins 70° rigid telescope (Karl Storz 7200C) (Fig 1A); 3) a xenon cold light fountain (Karl Storz 487C) and a Pilling 2X Luminator; 4) video cameras [1) an Elmo EM-102 micro CCD color video camera (15 lux) (Fig 1B) attached to the flexible fiberscope; 2) a Ricoh CCD R-620 home color video camera (4 lux) (Fig 1B) attached to the Hopkins 70° rigid telescope; and 3) an Ikegami professional camera, to videotape the overview picture of the procedure] and two monitors placed side-by-side showing the simultaneous images of the soft palate and the larynx; 5) Sony $^3/_4$-in VO-5600 and VO-5800 video recorders; 6) an Electro-voice RE-10 unidirectional microphone; 7) a Sony UP-811 videographic printer; and 8) a Kay Elemetrics DSP Sona-Graph, model 5500.

Technique. The subject sat facing the examiner and the assistant (Fig 1C). Topical anesthesia and vasoconstriction were achieved with aerosolized 4% lidocaine hydrochloride (Xylocaine) and 3%

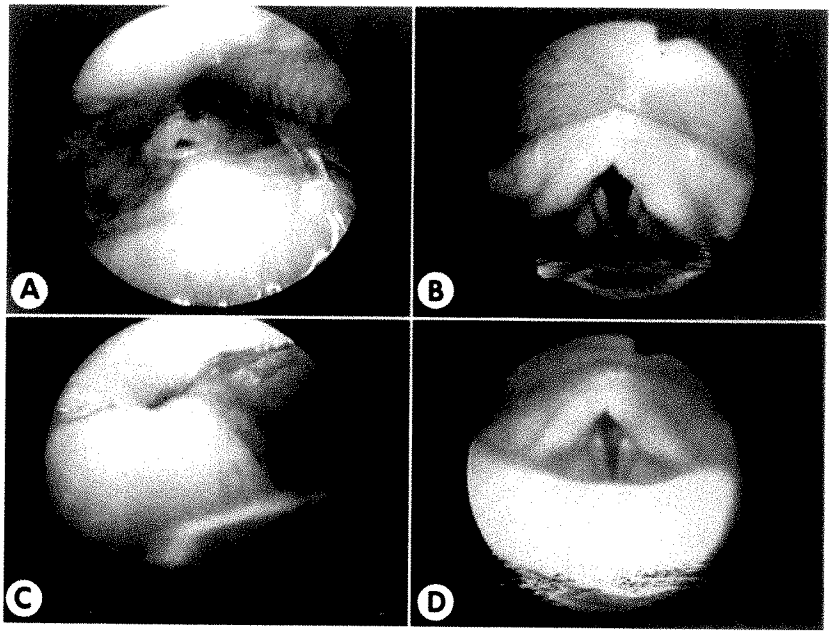

Fig 2. Respiration. A) Telescopic view of nasal respiration showing wide open velopharyngeal port. B) Fiberscopic view of nasal respiration at larynx, simultaneous with A. C) Telescopic view of oral breathing, showing closure of velopharyngeal port. D) Fiberscopic view of larynx, simultaneous with C.

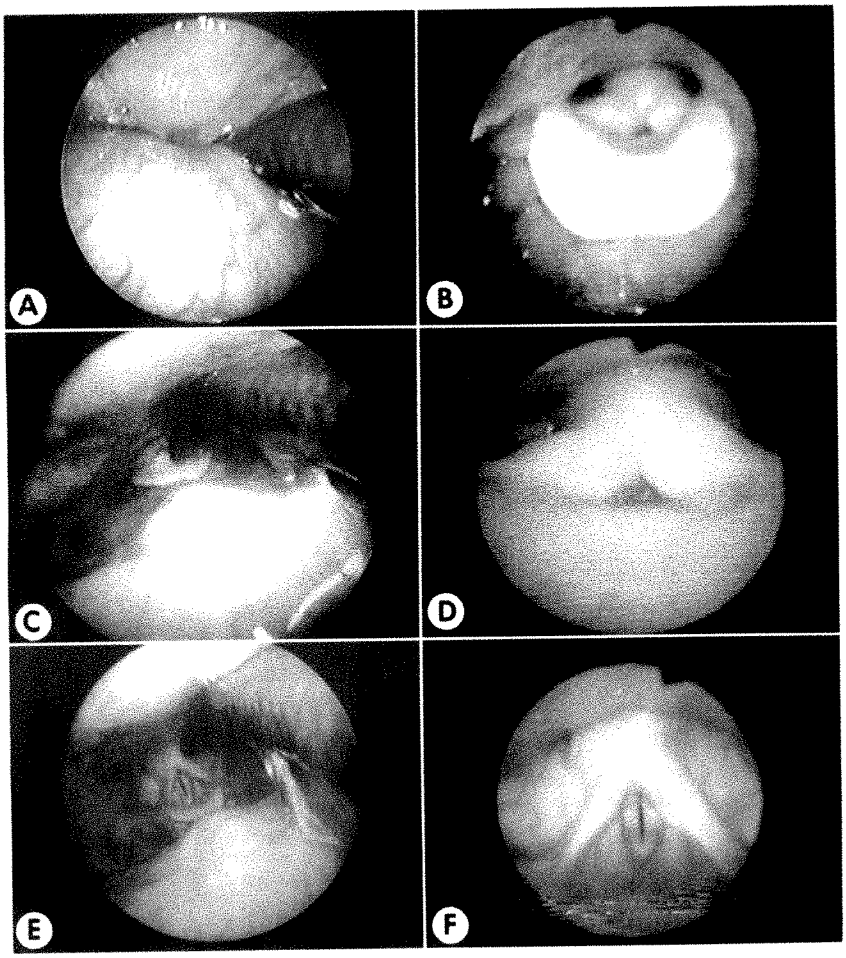

Fig 3. Effort closure. A) Telescopic view of onset of coughing, showing raised soft palate and tight velopharyngeal port closure. B) Fiberscopic view of larynx, showing constricted aryepiglottic sphincter, simultaneous with A. C) Telescopic view of straining, showing wide open velopharyngeal port. D) Fiberscopic view of larynx, showing marked constriction of aryepiglottic sphincter, simultaneous with C. E) Telescopic view of laughing (on /a/), showing wide open velopharyngeal port. Note larynx in full view. F) Fiberscopic view of larynx, simultaneous with E.

ephedrine sulfate. In addition, a pledget soaked with 4% lidocaine solution and 3% ephedrine was placed for 5 minutes in the right side of the nasal cavity, which was used to pass the rigid telescope. No injected anesthetic was required.

Simultaneous velolaryngeal videoendoscopy was performed as follows. The Olympus ENF-P flexible fiberscope was first passed through the left nasal cavity. After the nasopharynx and the soft palate were carefully examined, the fiberscope was passed down to the pharynx. When the ideal image of the larynx was obtained on monitor 1 (fiberscopic image), the fiberscope was fixed to the nose with adhesive tape. The fiberscope, to which the first video camera was attached, was then handed over to the assistant who held the fiberscope and the camera during the entire procedure. The Hopkins 70° rigid telescope, to which the second video camera was attached, was then passed into the right nostril. While viewing monitor 2 (the telescopic image), the operator carefully and slowly passed the scope into the nasopharynx between the inferior turbinate and the nasal septum, and the optimal image of the upper surface of the soft palate and the velopharyngeal sphincter was obtained.

Normal laryngeal functions studied included 1) respiration (oral and nasal), 2) glottal effort closure (straining, coughing, etc), 3) swallowing, and 4) phonation. Phonatory tasks consisted of 1) reciting the alphabet, 2) counting, 3) connected speech, and 4) whistling. For the singers, the additional tasks consisted of 1) /m/ to nasal vowels, 2) /ng/ to oral vowels, 3) a scale sung on /ng/, and 4) a complex five-part vocal figure containing five voice qualities. The five-part singing task began with 1) a totally nasalized /ng/ and progressed to 2) a nasalized /i/, 3) a nasalized /i/ in twang quality, 4) an oral /i/ in twang quality, and 5) an /i/ in which the oral twang quality was modified by lowering the larynx. The first three segments were all nasal; the last two, oral. With the simultaneous endoscopic procedure, it was possible to verify that in the first three conditions, the qualities were indeed nasal, while in the last two conditions, in which the velopharyngeal port was closed, the qualities were oral.

During the videotaping procedure, three separate images were recorded on three separate ¾-in video cassettes. The three views obtained consisted of 1) the telescopic view (monitor 1), 2) the fiberscopic view (monitor 2) and 3) an overview of the study taken by the third camera, which included the simultaneous view of monitor 1 and monitor 2 (Fig 1C). All the recordings were made on the Sony ¾-in VO-5600 recorders. The audio signals were si-

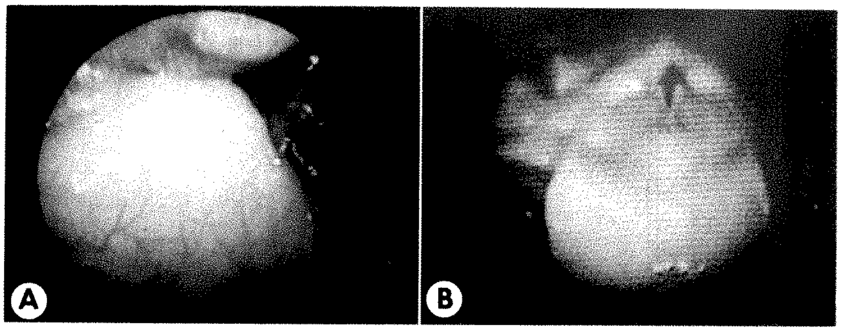

Fig 4. Whistling. A) Telescopic view showing elevation of soft palate with complete closure of velopharyngeal port. B) Fiberscopic view of larynx, simultaneous with A, showing slightly open glottic space.

Following the videotaping session, the recorded videotapes were taken to a professional editing facility, where the telescopic image of the soft palate and the fiberscopic image of the larynx were combined onto a single cassette tape. Synchronization of both images was accomplished by matching the audio signal from both tapes. The third camera, which recorded the activities of the other two cameras simultaneously, was used to check the accuracy of later synchronization.

Hard copies of representative velar and laryngeal images during normal laryngeal functions were made with the Sony videographic printer UP-811. Velar-laryngeal functions were also studied in slow motion with a Sony VO 5800 player. An acoustic analysis was made of the selected voice qualities in the five-part figure with the Kay Elemetrics DSP Sona-Graph, model 5500.

RESULTS

The first observation noted with dual endoscopy was the wide excursion of the flexible fiberscope in the nose as the soft palate opened or closed the velopharyngeal port. The vertical and/or dorsal movement of the larynx appeared greater when the fiberscope was passed along the floor of the nasal cavity than when it was passed along the middle meatus or above the septal spur. In the latter situation, the fiberscope was found to stay along the posterior wall of the nasopharynx, thus minimizing the "pseudolaryngeal" movement due to soft palate motion (Fig 2A).

Breathing. In nasal breathing, the soft palate was lowered and the velopharyngeal port was open (Fig 2A). In oral breathing, the soft palate was raised, narrowing the velopharyngeal port (Fig 2C). In both oral and nasal breathing, the glottic space was open (Fig 2B,D).

Coughing. With the dual scopes (in all but four subjects, who had an open port), the soft palate was up and the velopharyngeal port was closed; in preparation for the expulsive phase of the cough, the subglottic pressure rose and the supraglottic structures constricted (Fig 3A,B). As the air pressure of the cough escaped through the mouth, the soft palate lowered and the velopharyngeal port opened.

Straining. The soft palate was moderately raised during straining, but the velopharyngeal port was open in all our subjects (Fig 3C). The constriction of the aryepiglottic sphincter was a consistent finding (Fig 3D).

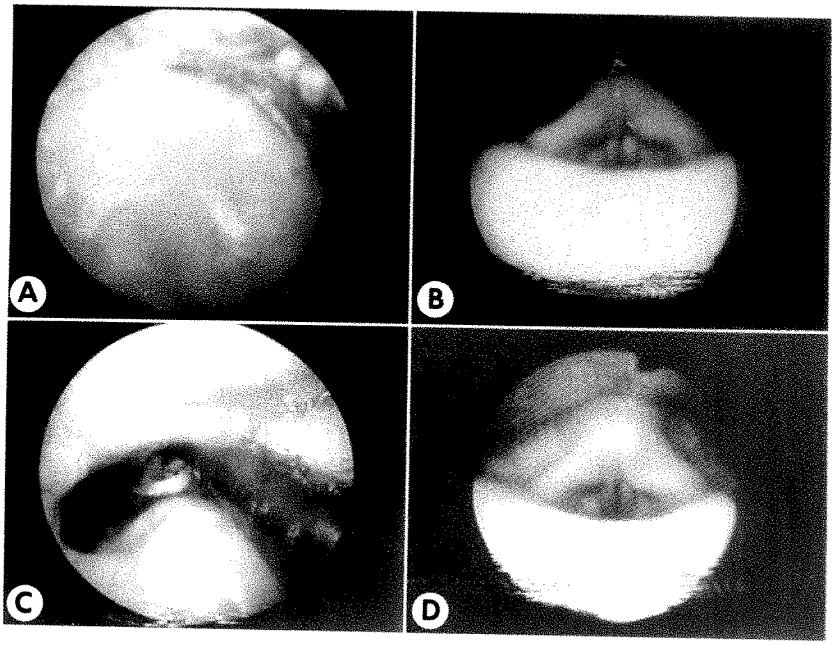

Fig 5. Phonation. A) Telescopic view showing elevation of soft palate with complete closure of velopharyngeal port during production of letter "K." B) Fiberscopic view showing larynx on letter "K," simultaneous with A. C) Telescopic view showing depression of soft palate with wide open velopharyngeal port on saying letter "M." D) Fiberscopic view of larynx on "M," simultaneous with C.

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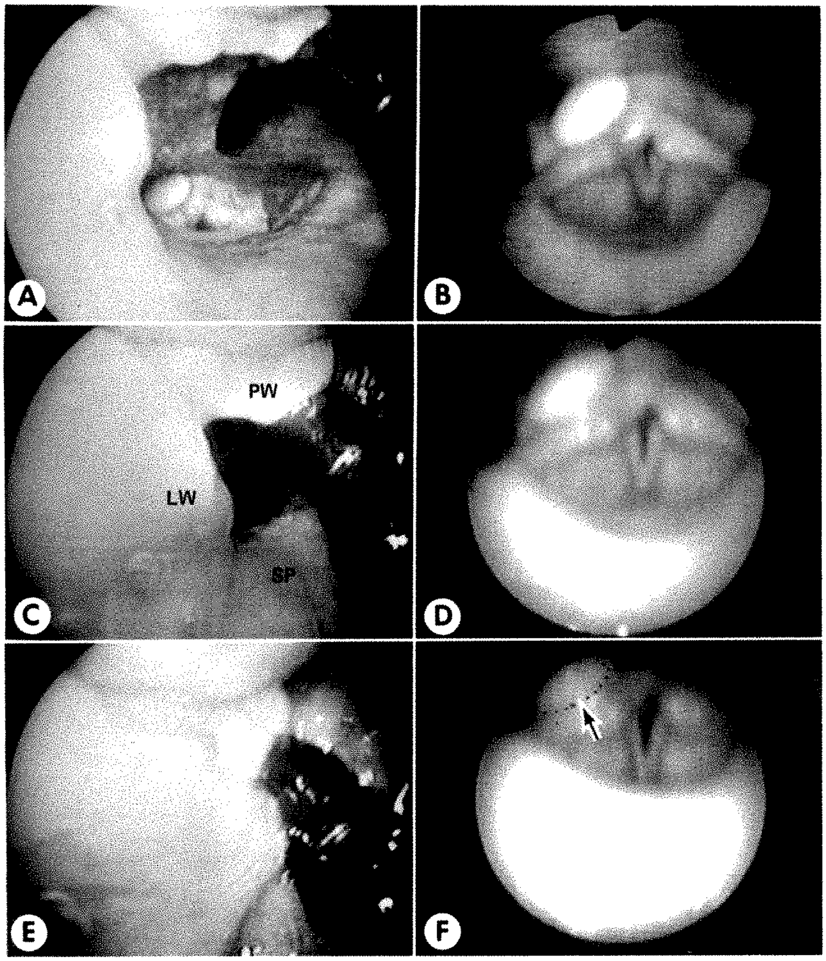


Fig 6. Swallowing (one cycle). A) Telescopic view showing pill in right pyriform sinus, as seen from wide open velopharyngeal port. B) Fiberscopic view of larynx showing pill in pyriform sinus, simultaneous with A. C) Telescopic view showing partial closure of velopharyngeal port. Note anterior displacement of posterior wall (PW), medial displacement of lateral wall (LW), and posterior superior displacement of soft palate (SP). D) Fiberscopic view of larynx showing vertical tilt of pill, simultaneous with C. Note open glottis. E) Telescopic view showing closure of velopharyngeal port. Note marked medial movement of lateral wall. F) Fiberscopic view of larynx showing further downward movement of pill (arrow). Note enlargement of epiglottis as larynx rises, and movement of epiglottis to cover vocal folds, simultaneous with E. (Continued on next page.)

Laughing. With laughing there was a convulsion in the soft palate comparable to that observed in the larynx (Fig 3E,F). The velopharyngeal port was open in all cases (Fig 3E), but this appeared to be vowel-dependent. When the subject laughed on /i/, the soft palate was high and the port opening small. When the laugh was on /a/, the soft palate was lower and the opening larger.

Whistling. In all subjects, the soft palate was raised and the velopharyngeal port was closed throughout the whistle (Fig 4A). The involvement of the soft palate and the larynx in the production of whistling, in addition to the lips, was well documented (Fig 4).

Phonation. On inserting a fiberscope, it is customary for a clinician to ask the subject to produce a /ke/ to verify the location of the tip of the fiberscope in relation to the soft palate (Fig 5A,B). In all subjects, the soft palate was markedly elevated, with complete closure of the velar port, both for the phoneme /k/ and for the subsequent vowel /e/. In Fig 5A, it is clear the soft palate is firmly closed with production of the letter "K."

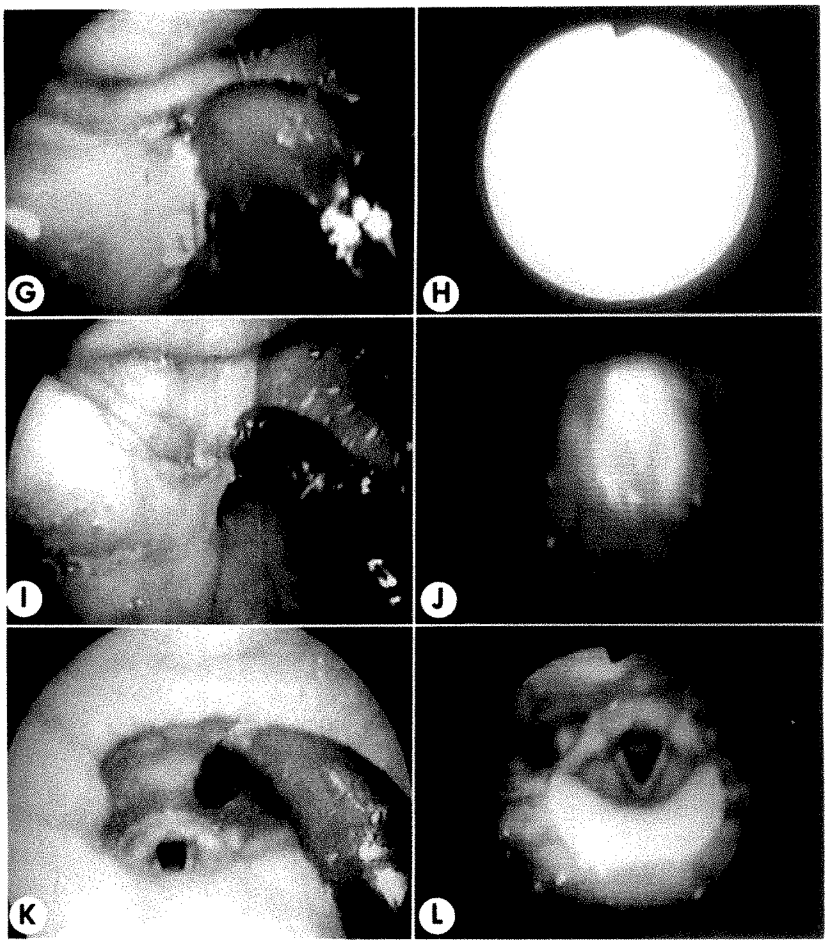
When the subjects recited the alphabet, there were two letter names, M, /ɛm/, and N, /ɛn/, for which the soft palate was down with a wide open port for all subjects (Fig 5C). For some subjects, when they recited the letters I and R, the port was slightly open. For all other letter names, the port was closed. Glottal approximation for all vocalizations could be well observed with simultaneous videoendoscopy (Fig 5B,D).

Swallowing (Fig 6). At the moment of swallowing, the velar port was closed. With the dual scopes, however, the dynamic action of the soft palate as well as that of the tongue, the pharynx, and the larynx during swallowing could be well observed. The complex motion of the tongue during the preparatory phase of swallowing and the vertical excursion of the epiglottis also could be documented on some patients (Fig 6J).

Voice Quality. There were two initial observations with the singer subjects: when the soft palate was raised sharply, the rigid scope sometimes was occluded, and the larynx did appear to shift dorsally. When the oral tone was made nasal by opening the port maximally, the larynx seemed to lower somewhat as the tone lost its clarity and became nasal.

In the five-part vocal figure, the sequential changes in quality could be noted, from a completely nasal to a rather loud oral tone by specific

Fig 6, continued. G) Telescopic view showing tight closure of velopharyngeal port. Note closure by all components of velopharyngeal sphincter. H) Fiberscopic view showing complete "whiteout" of fiberscope by constriction of faucial isthmus at actual moment of swallowing, simultaneous with G. I) Telescopic view showing beginning of apparent relaxation of velopharyngeal sphincter. J) Fiberscopic view of larynx showing upward and backward movement of epiglottis (to its normal position), simultaneous with I. K) Telescopic view showing wide open glottic space as seen from wide open velopharyngeal port immediately after swallowing. L) Fiberscopic view of larynx after swallowing, simultaneous with K.



changes in the condition of either the soft palate and/or the structures in the vocal tract below.

An acoustic analysis was made of the five-part figure. The changes in physiology and the effects of these changes on the acoustic spectra are shown in Fig 7. Eight seconds of time are displayed on the abscissa of each narrowband sonagram, and frequency to 8 kHz is displayed on the ordinate. Horizontally, the figure is in five parts, corresponding to the five parts of the vocal maneuver: 1) /ng/, as in the "ng" of [sing], and totally nasal, 2) a nasalized /i/, 3) a nasalized twang on /i/, 4) an oral twang on /i/, and 5) an oral twang on /i/ with the addition of a lowered larynx.

In the upper left in each figure is a power spectrum taken at the vertical marker in the narrowband display below it and averaged over 50 ms of time. On the abscissa, frequency is displayed in kilohertz. Relative amplitude is displayed on the ordinate. The spikes from left to right in the power spectrum denote the fundamental frequency of the tone (415 Hz or A flat above middle C) and all its significant overtones.

The vertical dashed line in the upper left power spectrum and the horizontal dashed line in the narrowband display below are the 3-kHz markers indicating the area in the spectrum in which high amplitudes will result in the perception of a loud, "ringing" tone. In the upper right corner are both the soft palate image taken with the 70° rigid scope and the laryngeal view of the larynx taken with the flexible scope. The power spectrum and the corresponding pictures were taken well beyond the onset of each new condition.

The /ng/ contained only two partials (Fig 7A). The mouth was closed as the velum and tongue functioned to create this totally nasal sound. The port was open, and the vocal folds were exposed to view.

In the second segment (Fig 7B), the soft palate flattened somewhat as the tongue moved from the velar /ng/ to the frontal vowel /i/. The vocal folds appeared now to have lengthened, or at least to have become more exposed to view, and/or the larynx might have tilted dorsally. Both the narrowband spectrum and the power spectrum displayed the antiresonance of nasality in the area of 1,500 Hz.

In the third segment (Fig 7C), the subject constricted the aryepiglottic sphincter to generate a twang quality, nasalized. The soft palate also constricted, but the velopharyngeal port was still patently open. When the sound changed to a metallic, nasal twang quality, changes in the spectrum were

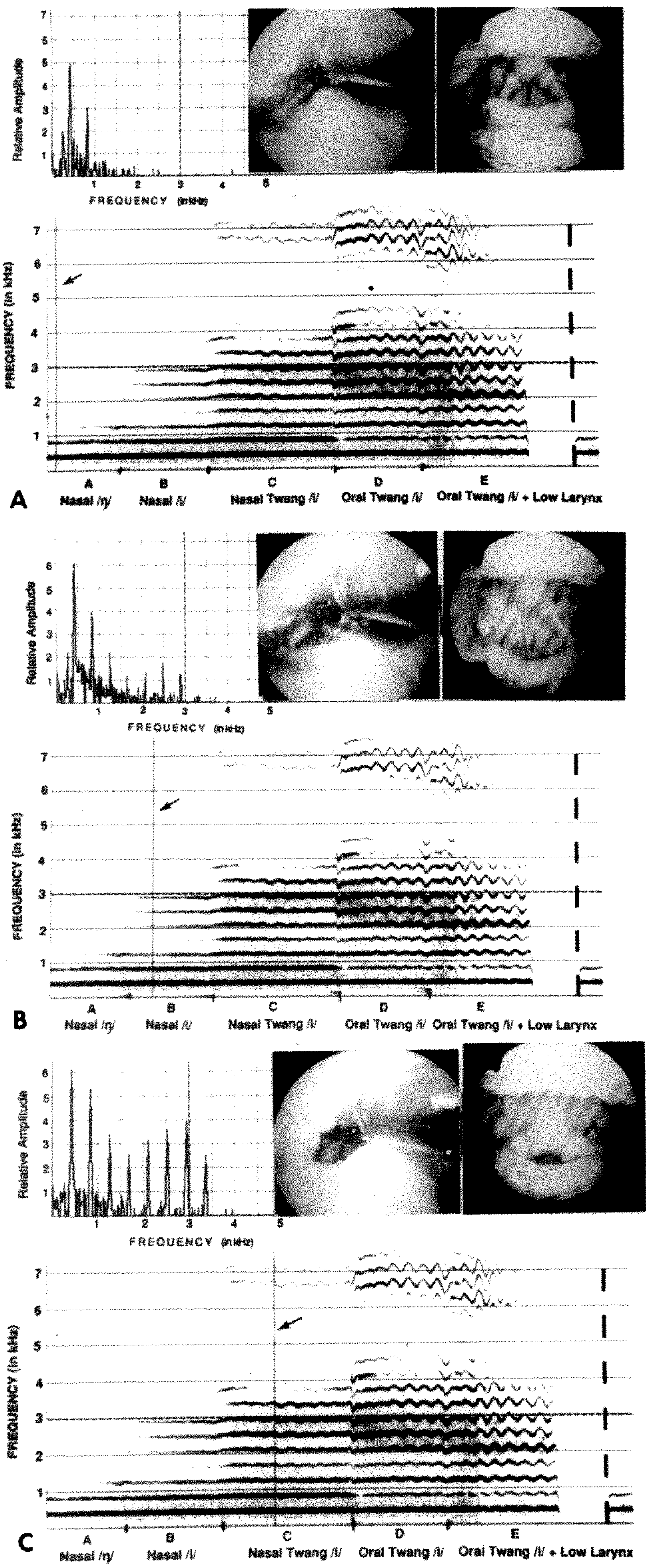


Fig 7. Simultaneous endoscopic pictures and acoustic analysis of each of five segments of vocal sequence containing three nasal and two oral voice qualities. Left endoscopic photograph in each figure shows superior surface of soft palate taken with Hopkins 70° rigid telescope. Right photograph is of larynx as seen by flexible fiberscope. Lower bar graph is narrowband spectrum over time (8 seconds). In upper left is power spectrum averaged over 50 ms at cursor (arrow) in bar graph below. A) Cursor is at far left over nasal sound /ng/ at 415 Hz (A flat above middle C). Soft palate is high and velopharyngeal port is open. B) Cursor is over nasalized /i/. Palate is lower and velopharyngeal port is open. Folds are more exposed. C) Cursor is over sound of nasal twang on /i/. Velar port is open, but aryepiglottic sphincter has contracted as arytenoids and epiglottis approximate each other. (Continued on next page.)

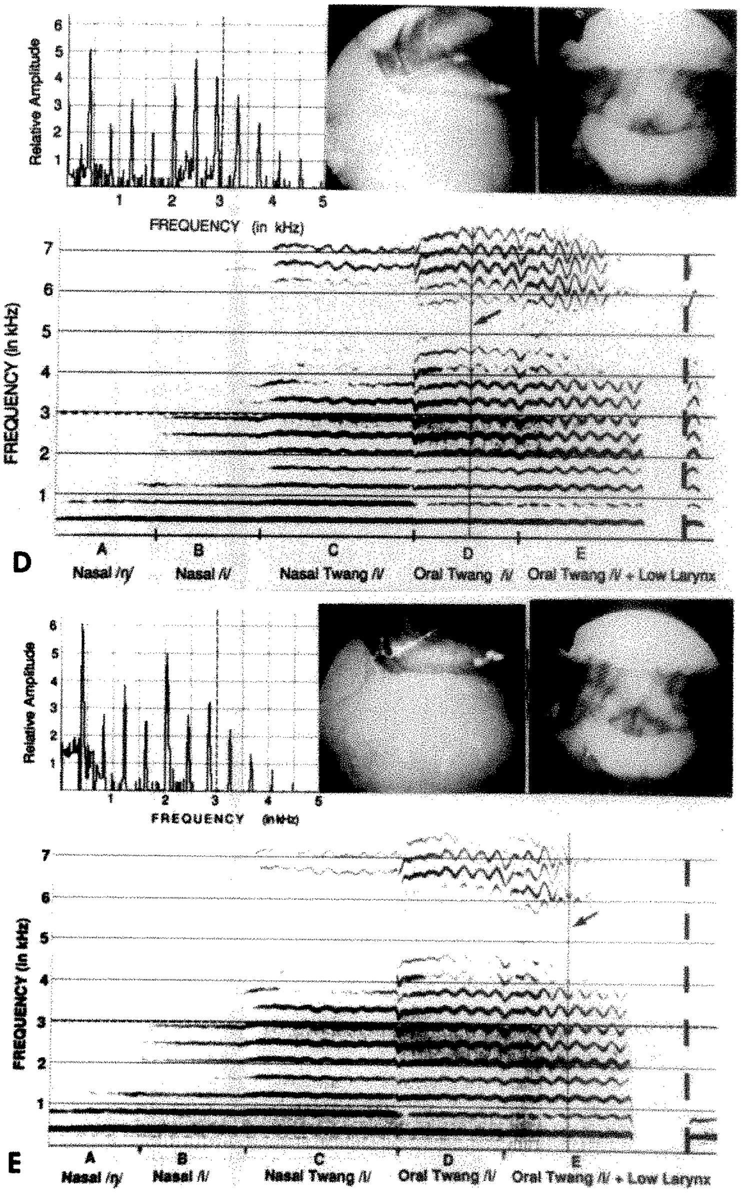


Fig 7, continued. D) Cursor is over sound of oral twang on /i/. Velar port is tightly closed around flexible scope, while aryepiglottic sphincter is unchanged. E) Cursor shows oral opera quality in which velar port remains closed and part of aryepiglottic constriction remains, but larynx is lower.

quite marked. The first and second partials were nearly equal in amplitude, the first having lowered from the nasalized /i/ condition and the second having lifted. All the other partials were also higher than in the nasalized /i/ condition, with partial 7 more than three times higher. Formant 2 appears to have shifted upward, from 2,490 Hz to 2,905 Hz. The endoscopic pictures confirmed that the nasal cavity and oral pharynx were still coupled.

The velopharyngeal port was abruptly closed, as can be seen by the vertical glitch in the narrowband spectrum at the beginning of the fourth segment (Fig 7D). The port was tightly closed around the flexible scope, and the aryepiglottic sphincter remained constricted. The difference in the spectrum was in the addition of some higher partials and a shift in amplitude of the lower partials. There was now increased energy at partials 9, 10, 11, 16, and 17, or up to 7,055 Hz. The partials in the 2- to 3-kHz range were almost of equal amplitude.

In the final segment (Fig 7E), the velopharyngeal port remained closed; the aryepiglottic constriction was still evident in the anterior position of the arytenoids, but the larynx had lowered and was more open to view. The acoustic consequence was a change in the relationship of the amplitudes of the partials, and a lowering of the frequency of formant 2 from 2,490 Hz in Fig 7D to 2,000 Hz in Fig 7E.

Looking at all five segments displayed on the sonagram, it can be noted there was evidence of vibrato shown as early as Fig 7C, becoming stronger in Fig 7D and quite marked by Fig 7E. Vibrato was also observed in the soft palate and in the vocal tract during videotaping. Since vibrato was not the focus of this study, it will be discussed only briefly below.

DISCUSSION

Simultaneous velolaryngeal videoendoscopy is a useful technique to study the soft palate and larynx and the interactions of these two complex structures during various selected physiologic functions.

LARYNGEAL FUNCTION

Breathing. In nasal breathing, the soft palate is down with a wide open velopharyngeal port (Fig 2A). In oral breathing, the soft palate is up and the velopharyngeal port is narrowed or even closed in some individuals (Fig 2C). This observation reinforces the teaching that transoral mirror examination of the nasopharynx and, additionally, passage of the flexible fiberscope through the tight velopharyngeal port is facilitated by nasal breathing, which opens the velopharyngeal sphincter.

Coughing. Coughing is a reflexively triggered response to clear the lower airway of irritating agents and foreign bodies. This function necessitates the generation of a significant subglottic airway pressure by thoracic contraction against a closed glottis, followed by a sudden abduction of the vocal cords and a forceful release of air through the mouth. Not surprisingly, we find that the soft palate is raised and tight closure of the velopharyngeal port occurs during this pre-expulsive phase (Fig 3A,B), following which the port opens with the release of air through the mouth.

Straining. In theory, one would not expect velopharyngeal closure during "strain," because tight laryngeal closure would prevent airflow from the lungs into the supralaryngeal airway. With simultaneous videoendoscopy, one can see that the theory is correct, that there is little interaction of the soft palate with the larynx during straining, and that the velopharyngeal port does remain open (Fig 3C,D).

Laughing. Simultaneous videoendoscopy reveals that laughing involves the soft palate as well as the larynx. Whether the palate is higher or lower in laughing depends on the vowel in the laugh.[20,21] A "hah" sound will lower the palate as the tongue shapes the back vowel /a/ (Fig 3E,F). Conversely, in forming the "hee" sound, the tongue will rise as it forms the /i/, lifting the soft palate as well.

Whistling. The production of whistling is similar to that of a vocalized labial consonant in that intermittent bursts of air are released from the glottis dependent on the duration of the sound required. This burst of air passes through the vocal tract and is modified at the mouth, where it passes through another constriction at the lips. The escape of air through the nose is undesirable, and we observe that the velopharyngeal port is tightly approximated during this act (Fig 4).

Swallowing. Swallowing is a complex act, the components of which have been well described by many authors. The oral preparatory phase of swallowing is under conscious control and consists simply of mastication and preparation of the bolus against the hard palate with subsequent movement of the bolus posteriorly. In the pharyngeal phase of the normal swallowing maneuver, the velopharyngeal port closes as the larynx is elevated and the cricopharyngeus relaxes, resulting in the opening of the esophagus. With the rigid scope, one can see the soft palate rise to close the port (Fig 6A,C,E,G). The flexible scope inserted transnasally and advanced below the palate shows the other components of this phase of swallowing Fig 6B,D,F,H), namely, closure of the false folds, constriction of the aryepiglottic sphincter, elevation of the entire larynx beneath the base of the tongue, and the posterior caudal movement of the epiglottis.

Simultaneous velolaryngeal videoendoscopy is of significant value for the understanding of the swallowing mechanism (Fig 6). One of the unexpected findings was that the 70° telescope revealed in some subjects a clear view of the larynx through the wide open velopharyngeal port. The illumination from the flexible fiberscope even facilitates the visualization of the laryngeal image. Fig 6A shows a transnasal telescopic image of a pill in the pyriform sinus as seen through an open velopharyngeal port. Dual scope endoscopy shows that the "whiteout" of the fiberscopic view during the actual swallow is due to the constriction of the faucial isthmus by the posterior pharyngeal wall, the base of the tongue, and the elevated larynx (Fig 6H).

Phonation. It is no surprise to learn that the velopharyngeal port is open for the letters M (Fig 5C) and N in all subjects. The fact that in some subjects the port is slightly open on the letters I and R can be explained by the position of the tongue in making these two sounds. When the jaw drops to make the initial low back vowel sound of /a/ to say I or R, the soft palate may be lowered with the action of the palatoglossus muscle, much as it is with the distinctions between "hah" and "hee" in laughing.

VOICE QUALITY

In any standard dictionary, in many of the speech and hearing texts, and in books on vocal pedagogy, twang quality is defined as excessive nasality or hypernasality, and the general perception is that it is made in the nose. In singing, twang is most often heard in hillbilly or country-western music and, in speech, it sounds much like the quack of a duck.[22,23]

The percept of cleft palate speech is one of dullness. When "brightness" is part of the perception of a "nasal" quality, the brightness must have been created somewhere other than in the nasal cavities.[22,24-26] "Brightness" is associated with higher amplitudes in the upper partials, particularly in the 2- to 3-kHz range of the spectrum.[27,28]

In Fig 7A, the totally nasal sound of /ng/ has only two partials at a very low frequency.[29] In Fig 7B, for the nasalized /i/, there is an increase in acoustic energy in the second partial near 1,000 Hz and a flattening of acoustic energy near 2,500 Hz, where one would expect to find a higher resonance (formant 2) for /i/ if it were not nasalized.[30,31] In the nasalized twang quality (Fig 7C), the increase in the amplitude of the partials in the 3-kHz range is due to the constriction of the aryepiglottis. When the aryepiglottic sphincter is constricted, it creates an extra resonator between the aryepiglottic rim and the vocal folds. Because of its small length, theoretically about 3 cm, the resonator will raise the partials in the 3-kHz range.[22,25,26,32] In Fig 7D, adjacent partials are almost equal in amplitude in the 2- to 3-kHz range, contributing to the perception of a "buzz" or metallic quality in the twang sound.[33] When the larynx is lowered (Fig 7E), the odd partials are higher in amplitude than the even partials, contributing to the perception of a fuller tone.[28] Partials 4 through 10 are slightly lower in frequency, and formant 2 appears to have shifted downward from 2,500 Hz to 2,000 Hz, further adding to the perception of a darker tone.[34,35]

Thus, with the dual scope procedure, the difference between nasality and twang becomes clear. Twang is a quality generated by constriction of the aryepiglottic sphincter (Fig 7C). It can be nasal as in Fig 7C or oral as in Fig 7D. Acoustically, twang is accompanied by an increase in amplitude of the partials in the 3-kHz area of the spectrum, associated with the "ringing" sensation of "good" opera quality or of a vocal tone that projects. Nasality is characterized by a reduction in amplitude of the partials in the 1- to 2-kHz range of the spectrum and the absence of any great energy in the upper partials.

Vibrato was noted acoustically in Fig 7C-E and also while videotaping, both in the soft palate and in the vocal tract. We speculate that the presence of vibrato may be related to increased muscle tremor associated with increased muscular effort when additional structures are moved with each succeeding condition in the five-part vocal figure.

SUMMARY AND CONCLUSION

1. Simultaneous velolaryngeal videoendoscopy is a useful technique for studying and understanding the role of the soft palate during physiologic functions of the larynx.
2. The soft palate passively or actively participates in the physiologic and associated functions of the larynx, such as respiration, coughing, laughing, whistling, swallowing, and phonation.
3. Simultaneous velolaryngeal videoendoscopy has clearly documented the difference in the production of two qualities, nasality and twang, both of which in the past have been described as "nasal."

ACKNOWLEDGMENT — The authors are indebted to Stephen P. Crump for his assistance in the use of the Kay Elemetrics DSP Sona-Graph, model 5500, at the offices in Pinebrook, New Jersey. His assistance in the use of this newest model not only saved considerable time, but assured the analyses of the five-part vocal figure would be as accurate as possible.

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PROLIFERATION AND DIFFERENTIATION CHARACTERISTICS OF NORMAL HUMAN SQUAMOUS MUCOSAL CELLS OF THE UPPER AERODIGESTIVE TRACT

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Normal human squamous mucosal cells of the soft palate, buccal surface, epiglottis, hypopharynx, floor of the mouth, and tongue were cultured in vitro in serum-free medium. In medium MCDB 153 containing epidermal growth factor, insulin, bovine pituitary extract, and 0.1 or 2.0 mmol/L Ca^{++}, squamous mucosal cells double every 24 hours. These cells then can be induced to arrest their proliferation reversibly by treatment with transforming growth factor–β or ethionine, and they can irreversibly growth-arrest during senescence or when cultured in growth factor–deficient medium containing 2 mmol/L Ca^{++}. The latter medium also induces differentiation, as does culture of cells in serum-containing medium. Serum-containing medium furthermore promotes extensive cell stratification and the formation of multilayered squamous mucosal tissue specimens that can be removed intact by Dispase treatment. These specimens represent potential autogenous mucosal grafts that can be used in patients who require reconstructive surgery of the oral cavity and oropharynx. Normal human squamous mucosal cells therefore closely resemble keratinocytes derived from the epidermis in the mechanisms that regulate proliferation and differentiation. This model cell system should facilitate future studies on upper aerodigestive tract squamous mucosal cell physiology and pathophysiology.

KEY WORDS — cell cycle, cell differentiation, cell proliferation, oral squamous mucosa.

INTRODUCTION

Stratified squamous epithelium is one of the most common cell types in the human body. The skin and upper aerodigestive system are lined by squamous epithelium that is differentiated to form a protective barrier between the body and the external environment. In the process of differentiation, these cells synthesize specific cytoskeletal proteins, form cross-linked envelopes, and lose their proliferative potential.[1] A variety of methods has been used to culture epidermal squamous cells, ie, skin keratinocytes.[2-7] Most of these methods have employed feeder layers of 3T3 cells or extracellular matrix preparations as a substrate for keratinocyte growth.[8-11] Peehl and Ham,[12,13] Ham,[14] and Tsao et al,[15] however, developed a defined nutrient medium, MCDB 153, that when supplemented with epidermal growth factor (EGF), insulin, and other factors supports the long-term proliferation of keratinocytes on tissue culture plastic without contaminating fibroblasts or other cell types. Studies have been performed with use of this medium to evaluate the mechanisms involved in the control of keratinocyte proliferation and differentiation, and it has been established that these processes are integrally regulated.[16,17] Furthermore, cultured epidermal keratinocytes have been used to generate epidermal grafts for transplantation in vivo.[18-22]

Very few previous studies, however, have focused on the culture of human squamous mucosal cells of the upper aerodigestive tract.[23-25] Those studies that have been performed were limited by the required use of 3T3 feeder layers, dimethyl sulfoxide, and/or fetal calf serum (FCS). For example, a recent report on mucosal squamous cells that employed dimethyl sulfoxide and FCS was limited because 20 to 25 days of incubation were required to generate enough cells to subculture.[25]

In the current report we employed defined methods to culture normal human squamous mucosal cells of the upper aerodigestive tract. The successful use of this experimental system has made it possible to establish 1) the proliferation and differentiation characteristics of squamous mucosal cells, 2) growth factor requirements of squamous mucosal cells, 3) the ability of squamous mucosal cells to growth-arrest, and 4) the ability of squamous mucosal cells to differentiate and stratify under specific microenvironmental conditions.

MATERIALS AND METHODS

Primary Cultures and Serial Subcultures. Human squamous mucosal cells were isolated from the epithelium of the oral cavity, oropharynx, and hypopharynx. Mucosal specimens were obtained from surgical waste materials and stored at 4°C in phosphate-buffered saline (PBS) for < 6 hours. The specimens were then trimmed of excess submucosal con-

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From the Section of Experimental Pathology (Scott) and the Department of Otorhinolaryngology (Kasperbauer, Neel), Mayo Clinic/Foundation, Rochester, Minnesota. Supported by the Mayo Foundation and National Institutes of Health grant CA 28240, Council for Tobacco Research grant 1750, and Eagles grant 81 to R.E.S.

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nective tissue, cut into fragments (approximately 4 mm^2), and placed in 0.17% trypsin at 4°C for approximately 16 hours. Thereafter, specimens were stripped from submucosal connective tissue and placed in a buffered saline solution containing 0.0375% soybean trypsin inhibitor.

The specimens were next triturated and filtered through Nitex mesh. After centrifugation, dissociated single cells were counted and subsequently plated on tissue culture plastic in complete MCDB 153 medium at approximately 5×10^3 $cells/cm^2$. They were then re-fed every other day and cultured in a humidified environment containing 5% carbon dioxide at 37°C. Penicillin (100 U/mL) and streptomycin (100 μg/mL) were included in the medium for the first 48 hours of primary culture. Although cells from all sites behaved similarly, the majority of data in this report comes from cells obtained from the oral cavity, more specifically from the soft palate.

Serial Passage. The method used to passage squamous mucosal cells is essentially the same as described previously.[26,27] First passage subcultures were initiated approximately 7 days after initial plating. All subsequent passages were performed before the cells reached a density of 1×10^4 $cells/cm^2$ except when indicated otherwise. Subcultures were typically reestablished at densities of 500 to 1,000 $cells/cm^2$.

Culture Media and Reagents. All cells were grown in MCDB 153 basal nutrient medium[28] supplemented with ethanolamine (0.1 mmol/L), phosphoethanolamine (0.1 mmol/L), hydrocortisone (5×10^{-7} mmol/L), Ca^{++} (0.1 mmol/L), insulin (5 μg/mL), EGF (10 ng/mL), and bovine pituitary extract (BPE; 140 μg/ mL) unless indicated otherwise. This medium is designated complete MCDB 153.

Hydrocortisone, ethanolamine, insulin, phosphoethanolamine, trypsin, soybean trypsin inhibitor, and bovine serum albumin (BSA) were purchased from Sigma Chemical Company (St Louis). Fetal calf serum was purchased from Hyclone Laboratories (Logan, Utah). Epidermal growth factor was purchased as culture grade from Collaborative Research, Inc (Worcester, Mass). Whole bovine pituitaries were obtained frozen from Pel-Freeze Biologicals (Rogers, Ark), and the extract preparation followed that described by Tsao et al.[15] Anti-human involucrin was obtained from Biomedical Technologies, Inc (Stoughton, Mass). Dispase was obtained from Boehringer Mannheim (Indianapolis). ^{3}H-Thymidine (specific activity, 77.9 Ci per mmol/L) was purchased from New England Nuclear (Boston). Nitex mesh was purchased from Tetko Inc (Elmsford, NY). Transforming growth factor-β (TGF-β) was purchased from R and D Systems (Minneapolis).

Plating Efficiency, Colony-Forming Efficiency, and Clonal Growth Assays. Evaluation of clonal growth employed previously described methods[16,27] wherein 500 cells were plated per 60-mm Petri dish in complete MCDB 153 medium. The specimens were then incubated, and at appropriate times they were fixed and stained with crystal violet, and colonies were counted microscopically.

Plating efficiency (PE), calculated with use of specimens fixed after 24 hours of incubation, is expressed as the number of cells that attached in comparison to the 500 cells initially plated. Colony-forming efficiency (CFE), expressed as a percentage, is defined as the number of colonies of four or more cells that are evident after 10 to 12 days of incubation relative to the number of cells that plated within 24 hours.

DNA Synthesis and Reversible and Irreversible Growth Arrest. The extent of DNA synthesis was quantitated by measurement of ^{3}H-thymidine incorporation into DNA. Cell cultures were pulse-labeled for 1 hour with ^{3}H-thymidine at a concentration of 4 mCi/mL, and the amount of incorporation was quantitated by scintillation spectroscopy after trichloroacetic acid precipitation of DNA by a standard procedure.[29] The extent of DNA synthesis defined to be consistent with growth arrest was set as $\leq 5\%$ of rapidly growing control cultures.

Growth arrest can be induced by a variety of treatments, as described in Results. The reversibility of growth arrest was determined by the use of clonal growth assays. Reversible growth arrest was defined to exist when treated cells retained clonogenicity following reculture in complete MCDB 153. Irreversible growth arrest was defined as the loss of clonogenicity.

Cytofluorimetry. The distribution of cells in the cell cycle was determined by measurement of DNA content with a Becton-Dickinson FACS IV following mithramycin (1 ng/mL) staining of DNA.[30] Cell cycle analysis was performed by standard computer analysis.[31]

Cell Kinetics. Cell density measurements were performed by counting of cells in situ. Multiple randomly selected fields of a known surface area were evaluated with a phase-contrast microscope. From these data, cellular growth kinetics were determined.

Differentiation Assays. The characteristics used to assay cell differentiation were involucrin expression[32,33] and/or morphologic evidence of stratification and the formation of so-called "crowns."[34] Involucrin is a cellular protein that is expressed selectively in differentiated suprabasal squamous cells.[32] For these studies, involucrin was assayed by an indirect immunofluorescent staining method.[33] Briefly, a 40-μL suspension of 2.5×10^5 cells/mL in PBS containing 1% BSA was placed on a microscope slide and air dried. The slides were stored at

TABLE 1. ORIGINS OF SQUAMOUS MUCOSAL CELLS FOR IN VITRO CULTURE

Site of Origin	*No. of Specimens*
Oral surface of soft palate	5
Buccal mucosa	2
Epiglottis	1
Hypopharynx	1
Floor of mouth	1
Tongue	1

−20°C. Subsequently, the slides were fixed sequentially in 10% buffered formalin (8 minutes), methanol (4 minutes at −20°C), and acetone (2 minutes at −20°C). Specimens were then rinsed in a Tris-buffered saline solution (0.15 mmol/L NaCl, 0.01 mmol/L Tris chloride, pH 7.6). Sequential 30-minute incubations of specimens with normal goat serum, rabbit anti human involucrin, and fluorescein-conjugated goat anti rabbit IgG were performed by standard procedures.[33] The percentage of cells that stained for involucrin was determined with a Zeiss fluorescence microscope.

Stratification and Dispase Mobilization of Squamous Mucosal Cell Sheets. Both epidermal keratinocytes[16] and squamous mucosal cells require supplementation of complete MCDB 153 with the following agents to attain confluence: isoleucine (7.5 x 10^{-4} mmol/L), histidine (2.4 x 10^{-4} mmol/L), methionine (9 x 10^{-5} mmol/L), phenylalanine (9 x 10^{-5} mmol/L), tryptophan (4.5 x 10^{-5} mmol/L), and tyrosine (7.5 x 10^{-5} mmol/L). To induce stratification, such cultures near confluence were re-fed serum-containing media. The extent of stratification was determined by light microscopic examination of cross sections of paraffin-embedded specimens. Stratified specimens of squamous mucosal cells were removed as intact tissue sheets by incubation in Dispase[22] or were removed as single cells by trypsinization. The latter method was employed to prepare single cell preparations to evaluate involucrin expression.

RESULTS

Squamous Mucosal Cell Isolation and Culture. The isolation of squamous mucosal cells from a variety of tissues (Table 1) employed the overnight trypsinization of specimens at 4°C. As a result of this process, a single cell suspension of squamous cells was obtained. Figure 1A illustrates a representative section of squamous mucosa from which the cells were obtained. Figure 1B shows the appearance of this tissue after trypsinization with the presence of a cleavage plane between the epithelium and the basement membrane. Figure 1C illustrates

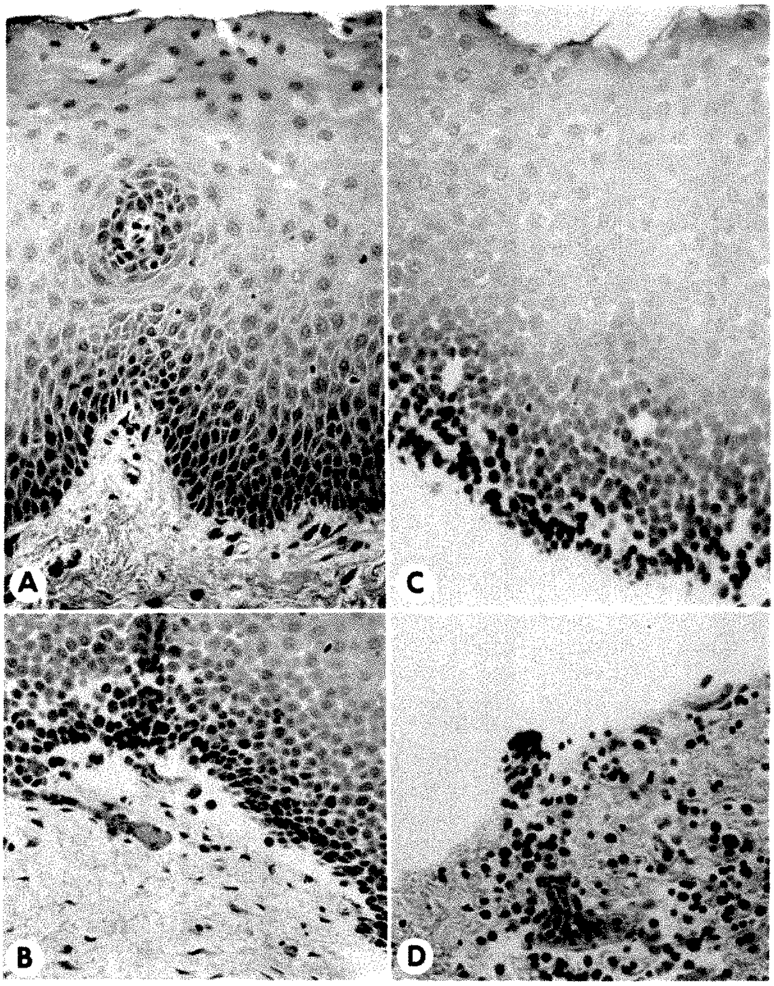

Fig 1. Microscopic demonstration of steps involved in preparation of oral squamous mucosal cells from tissue specimens. A) Representative section of intact oral squamous mucosa (original x290). B) Tissue specimen after overnight trypsinization prior to separation of mucosa from submucosa (original x310). Demonstrates cleavage plane between cells of basal layer and basement membrane. C) Section of squamous mucosa that has been separated from submucosa (original x290). Note that entire full thickness of squamous mucosa is removed. D) Section of residual submucosa after removal of squamous cells (original x290). (This illustration and Figs 2, 4, 6, and 7 have been reduced approximately 34% compared to originals.)

TABLE 2. REQUIREMENT OF EGF, INSULIN, PDGF, AND/OR BPE FOR SQUAMOUS MUCOSAL CELL CLONAL GROWTH

Polypeptide Additives	*Colony-Forming Efficiency (% Maximum)*
Insulin	7
EGF	1
BPE	0
PDGF	0
Insulin + EGF	91
Insulin + BPE	5
Insulin + PDGF	6
EGF + BPE	97
EGF + PDGF	92
PDGF + BPE	0
Insulin + EGF + PDGF	79
Insulin + EGF + BPE	100
Insulin + BPE + PDGF	3
EGF + BPE + PDGF	100

Assays were performed in MCDB 153 medium containing all factors described in Methods section plus indicated growth factors. Concentration of these polypeptide additives was fixed in these assays: insulin, 5 μg/mL; EGF, 10 ng/mL; BPE, 0.1%; and PDGF, 10 ng/mL.

EGF — epidermal growth factor, PDGF — platelet-derived growth factor, BPE — bovine pituitary extract.

a section of mucosa after it was separated from the submucosa, and Fig 1D illustrates the remaining submucosa devoid of the squamous epithelium. These photomicrographs demonstrate that with this trypsinization technique the entire thickness of the squamous mucosa can be harvested for culture. When a similar procedure is applied to fragments of skin, however, trypsinization initially induces a cleavage plane in the stratum spinosum, and only after more extensive trypsinization are all the squamous keratinocytes dissociated (M. S. Wilke et al, unpublished data).

Clonal assays initially were performed on dissociated cells to determine the percentage that attach and proliferate in vitro in primary cultures. By the methods described above, primary cultures of mucosal squamous cells demonstrated a 20% PE, and 25% of the cells that plated grew to form colonies. Therefore, of the cells isolated from the mucosal fragments, ≥5% formed proliferative primary colonies, and it is this population of cells that are characterized further in this study. Subsequent passage of these cells results in a >70% PE and a ≥90% CFE.

Growth Factor Requirements. Since complete MCDB 153 initially was developed to support the growth of epidermal keratinocytes, studies first were performed to evaluate whether insulin, EGF, platelet-derived growth factor (PDGF), and/or BPE in MCDB 153 medium optimizes growth of squamous mucosal cells. That is, clonal growth assays were performed in MCDB 153 with and without various additives, and the CFE was determined after 10 to 14 days' incubation. In these assays, all the media contained 0.1 mmol/L Ca^{++}. Clonal growth in response to each of these factors alone or in combination was first evaluated at fixed concentrations. These concentrations were insulin (5 μg/mL), EGF (10 ng/mL), PDGF (10 ng/mL), and BPE (0.1%). The results in Table 2 and Fig 2 demonstrate that EGF, insulin, PDGF, and BPE alone did not support significant clonal growth. Optimum growth was observed only with combinations of EGF and insulin; EGF and BPE/PDGF; or EGF, BPE, and insulin/PDGF. Attempts to increase clonal growth by varying the concentration of EGF, insulin, PDGF, or BPE did not produce a significant effect (data not shown). These results suggest that EGF is an absolute requirement for squamous mucosal cell growth, but that other factors such as insulin must also be present.

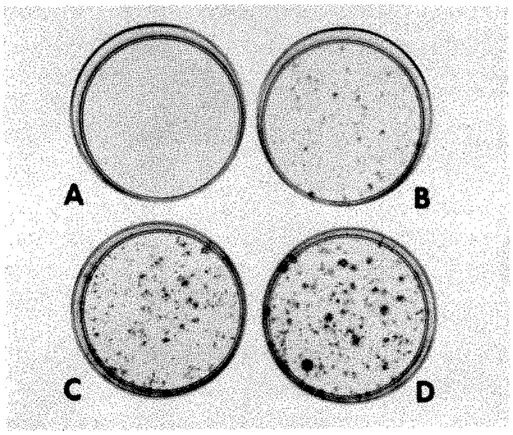

Fig 2. Representative specimens depicting various degrees of clonal growth in MCDB 153 containing different growth factor compositions. A) 0%. B) 35%. C) 75%. D) 100% maximum colony-forming efficiency.

Growth Kinetics. Figure 3 illustrates that squamous mucosal cells grow rapidly in complete MCDB 153, with a population doubling time of approximately 24 hours, and that such cultures attained a saturation density of approximately 2×10^4 cells/cm^2. Figure 4A is a phase contrast micrograph of a rapidly growing primary culture of squamous mucosal cells, and Fig 4B is a phase contrast micrograph of a similar culture that has reached a subconfluent saturation density in complete MCDB 153. If squamous mucosal cells are allowed to reach saturation density in complete MCDB 153 without amino acid supplementation, subsequent passage is decreased markedly. Studies performed with use of epidermal keratinocytes demonstrated similar findings.[12,17] However, when complete MCDB 153 is supplemented with additional amino acids prior to growth to high density, squamous mucosal cells continue to grow and reach a confluent cell density of approximately 1×10^5 cells/cm^2. Such cells furthermore retain the ability to be passaged.

Growth Arrest and Differentiation. Previous investigations on epidermal keratinocytes demonstrated that the control of cell proliferation and differentiation was regulated integrally and that

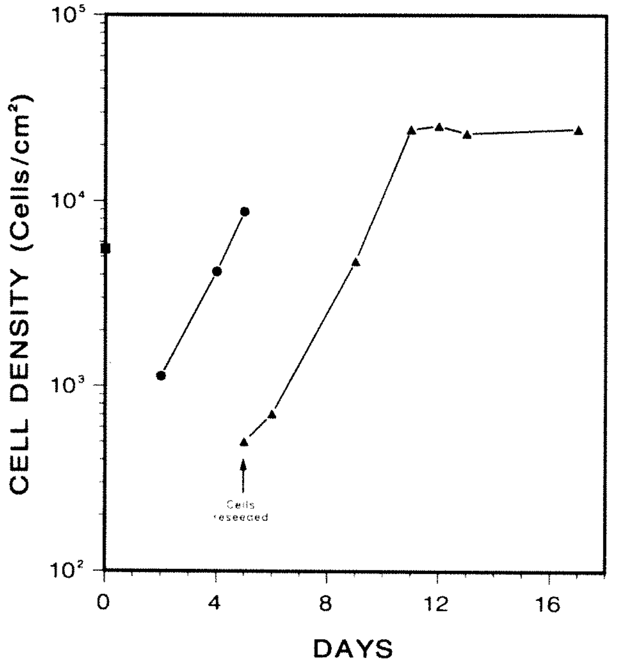

Fig 3. Representative growth curves of primary squamous mucosal cultures (●) and secondary cultures (▲) illustrating 24-hour population doubling time for both specimens. ■ — primary plating cell density.

growth arrest at various states is involved in the multistep process of differentiation.[16,17,33] To determine whether similar control mechanisms exist in squamous mucosal cells of the upper aerodigestive tract, we evaluated comparable growth arrest conditions. We also performed studies to determine if squamous differentiation (evaluated by involucrin expression and crown formation) is associated with growth arrest. The ability of cells to growth-arrest was determined by culture in 1) complete MCDB 153 containing TGF-β, 2) complete MCDB 153 containing ethionine, or 3) growth factor–deficient medium containing 2 mmol/L Ca⁺⁺ (GF-2). The arrest process was evaluated for reversibility by clonal growth assays. Cytofluorimetry was used to obtain cell cycle information related to these growth arrest states. Table 3 presents the data from these experiments.

The results show that reversible growth arrest occurs following TGF-β treatment and that such cells do not differentiate terminally unless they are cultured in medium containing 2 mmol/L Ca⁺⁺, at which time the cells express involucrin and lose their proliferative potential. The results also show that growth arrest in response to ethionine treatment is reversible initially, but that ethionine-arrested cells very slowly progress to terminal differentiation in medium containing 0.1 mmol/L Ca⁺⁺. This process of terminal differentiation can, however, be significantly enhanced by culture in medium containing 2 mmol/L Ca⁺⁺. The data in Table 3 also show that culture of squamous mucosal cells in GF-2 directly induces irreversible growth arrest and terminal differentiation. Squamous mucosal cells can also irreversibly growth-arrest in association with senescence. Table 4 summarizes these data and shows that both oral squamous cells and skin keratinocytes show similar growth arrest and differentiation characteristics.

Effect of Calcium on Cell Growth and Differentiation. To determine whether calcium concentration in the culture medium influences growth and differentiation in squamous mucosal cells of the upper aerodigestive tract, the characteristics of rapidly growing cells cultured in complete MCDB 153 containing 0.1 mmol/L, 1 mmol/L, or 2 mmol/L Ca⁺⁺ were compared. Figure 5 shows that comparable growth curves were obtained in all calcium concentrations. Furthermore, prior to reaching saturation density, none of the cells expressed involucrin, whereas after reaching saturation density, cells cultured in calcium concentrations greater than 0.1 mmol/L expressed involucrin (data not shown). These data together with those presented above suggest that in human squamous cells, high levels of calcium in the medium induce differentiation only in growth-arrested cells.

Cell Stratification and Differentiation. Studies next were performed to determine if squamous mucosal cell cultures could be induced to stratify in vitro. This is of potential clinical importance because of the need for autogenous mucosal grafts in

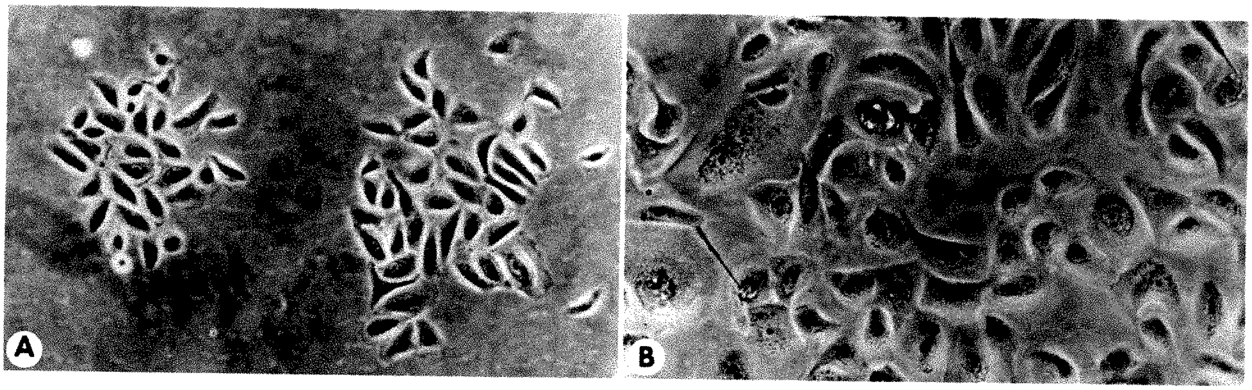

Fig 4. Phase-contrast micrographs. A) Rapidly growing low density squamous mucosal cells (original x190). B) High density squamous mucosal cells cultured in complete MCDB 153 (original x235).

TABLE 3. PROLIFERATION AND DIFFERENTIATION CHARACTERISTICS OF NORMAL HUMAN SQUAMOUS MUCOSAL CELLS UNDER THREE DIFFERENT CULTURE CONDITIONS

A. Growth Arrest Characteristics

Additive	*Time Required to Growth Arrest (d)*	*Cell Cycle Distribution (%)*			*Colony-Forming Efficiency After Growth Arrest (% Control)*
		G_1	*S*	*G_2/M*	
None (control)	—	50	25	25	100
TGF-β (5 ng/mL)	3	70	8	22	90
Ethionine (2 mmol/L)	2	64	15	21	95
GF-2	4	52	17	31	5

B. Differentiation Potential of Growth-Arrested Cells

Growth Arrest–Inducing Agent	*Terminal Differentiation**	
	Involucrin Expression	*Stratification and Crown Formation*
TGF-β (5 ng/mL)		
0.1 mmol/L Ca^{++}	0%	–
2.0 mmol/L Ca^{++}	42%	±
Ethionine (2 mmol)		
0.1 mmol/L Ca^{++}	1%	–
2.0 mmol/L Ca^{++}	44%	+
GF-2		
0.1 mmol/L Ca^{++}	ND	ND
2.0 mmol/L Ca^{++}	66%	+

ND — not determined.

*Involucrin expression is presented as percent cells that stain; crown formation was not numerically quantitated.

reconstructive surgery of the oral cavity and oropharynx. Stratification and subsequent autogenous grafting of epidermal keratinocytes has been accomplished and is of significant benefit in burn patient management.[18-22]

Techniques similar to those used to generate epidermal keratinocyte sheets[22] were applied to squamous mucosal cells. Rapidly growing cultures at near saturation density were re-fed amino acid–enriched complete MCDB 153 to induce growth to confluence. Subsequently, cells were re-fed one of the following media in an attempt to induce stratification with differentiation: Dulbecco's modified Eagle's medium (DMEM) + 10% FCS, DMEM + 30% FCS + insulin (5 μg/mL), or complete MCDB 153 + 10% FCS. Like epidermal keratinocytes, squamous mucosal cells stratify and differentiate in the presence of DMEM + 10% FCS or DMEM + 30% FCS + insulin. The latter medium induced the most prominent and uniform stratification. In contrast, culture of cells in complete MCDB 153 + 10% serum produced minimal stratification. Figure 6 illustrates squamous mucosal cell specimens stratified in DMEM + 10% FCS (Fig 6A) and DMEM + 30% FCS + insulin (Fig 6B). Stratification in the presence of serum also was associated with involucrin expression (data not shown). Stratified sheets of squamous mucosal cells represent a three-dimensional tissue specimen that can be mobilized by Dispase treatment (Fig 7). Such tissue specimens have the potential to be used as an autogenous transplant in vivo in reconstructive surgery of the oral cavity.

DISCUSSION

The data reported in this paper have potential significance from a biologic and clinical perspective. The clinical relevance of these results is derived from the observation that squamous mucosal cells can be cultured and induced to stratify and thereafter can be isolated as an intact three-dimensional specimen that has the potential for use as transplantable tissue for reconstructive surgery.

TABLE 4. SUMMARY OF BIOLOGIC CHARACTERISTICS SHARED BY NORMAL SQUAMOUS MUCOSAL CELLS AND EPIDERMAL KERATINOCYTES

Biologic Characteristic	*Treatment or Condition*	*Normal Squamous Mucosal Cells*	*Normal Epidermal Keratinocytes*
Reversible growth arrest in medium containing 0.1 mmol/L Ca^{++}	TGF-β treatment	+	+
	Ethionine treatment	+	+
Irreversible growth arrest in medium containing 0.1 mmol/L Ca^{++}	Senescence	+	+
Irreversible growth arrest and terminal differentiation in medium containing 2 mmol/L Ca^{++}	TGF-β treatment	+	+
	Ethionine treatment	+	+
	GF-2 treatment	+	+

TGF-β — transforming growth factor, GF-2 — growth factor-deficient medium containing 2 mmol/L Ca^{++}.

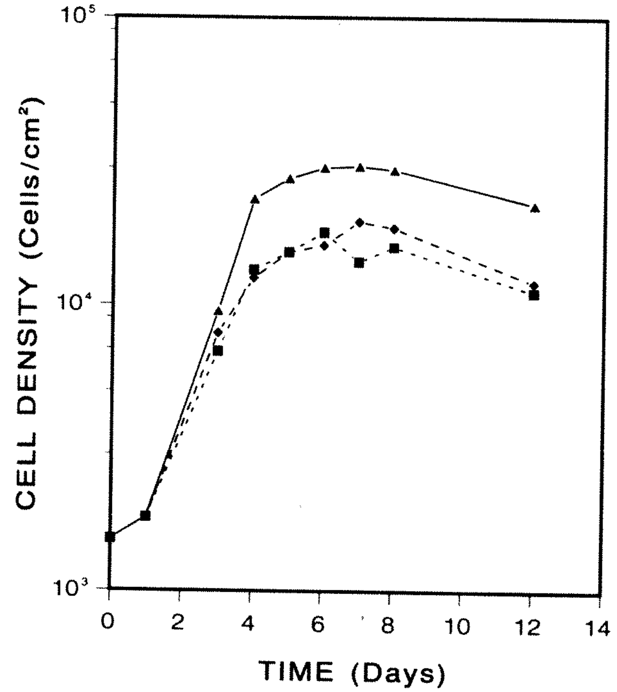

Fig 5. Effect of calcium concentration on squamous mucosal cell growth. No significant effect of calcium is evident on population doubling time of low density cells cultured in complete MCDB 153 containing 0.1 (▲), 1 (◆), or 2 (■) mmol/L Ca^{++}. Calcium concentration of 1 mmol/L and 2 mmol/L, however, resulted in slightly lower saturation density. High density cultures maintained in 1 or 2 mmol/L Ca^{++} demonstrated prominent differentiation after growth arrest at saturation density.

The biologic significance of these results is related to characterization of normal squamous mucosal cell proliferation and differentiation mechanisms.

The ideal physiologic in vitro cell culture system to study the proliferation and differentiation characteristics of normal human squamous cells does not exist. The system described in this paper, which employs serum-free complete MCDB 153 medium and standard tissue culture plastic flasks, nevertheless allows for the rapid growth of normal human squamous mucosal cells and their extensive subculture. In this cell culture system, it also is possible to evaluate the mechanisms that control squamous mucosal cell growth arrest and differentiation.

More specifically, the methods initially developed for the culture of normal human epidermal keratinocytes by Peehl and Ham,[12,13] Ham,[14] and Tsao et al[15] were extended to oral, oropharyngeal, and hypopharyngeal mucosal cells in the current experiments. In complete MCDB 153 medium, squamous mucosal cells grow rapidly and can be passaged with high efficiency. It also was established that squamous mucosal cells can be induced to undergo either reversible or irreversible growth arrest, and that following growth arrest, differentiation then can be induced by the addition of 2 mmol/L Ca^{++} and/or serum to the culture medium. In the latter medium, extensive stratification also was observed.

In epidermal keratinocytes,[16,17,33] the control of cell proliferation and differentiation is highly integrated. A model based on those studies suggests that three steps are involved in keratinocyte differentiation: 1) reversible growth arrest, 2) irreversible growth arrest, and 3) terminal differentiation.[33] The studies reported here show that similar mechanisms exist for squamous mucosal cells. In fact, epidermal keratinocytes and squamous mucosal cells share most in vitro characteristics in common (Table 4).

Since similar biologic mechanisms exist for the control of proliferation and differentiation of epidermal keratinocytes and squamous mucosal cells, it is meaningful to ask how such normal cells compare with metaplastic squamous cells derived from the human bronchial mucosa and with squamous carcinoma cells from the skin and oral cavity. Metaplastic human bronchial epithelial cells cultured in vitro[35-37] develop morphologic and histologic characteristics similar to those of keratinocytes, and they express specific keratins, cornified envelopes, and

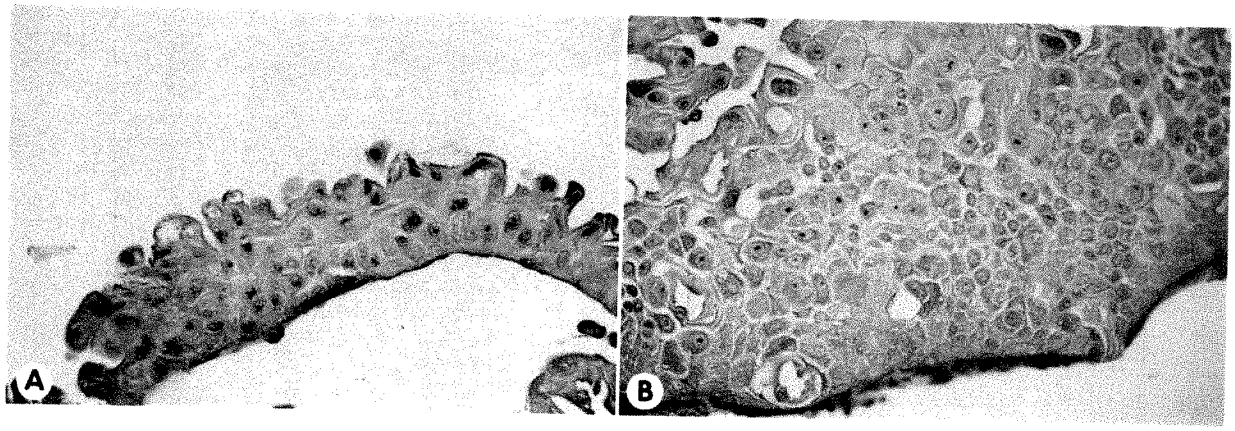

Fig 6. Photomicrographs of stratified squamous mucosal cells induced by different culture conditions. Bottom of each specimen of stratified cells represents cell–tissue culture flask interface. A) Stratification following 6 days of culture in DMEM + 10% FCS (original x290). B) Stratification following 7 days of culture in DMEM + 30% FCS + insulin (5 μg/mL) (original x300).

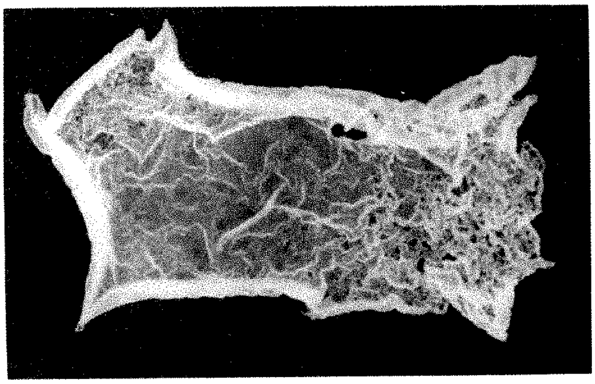

Fig 7. Photograph of stratified squamous mucosal tissue mobilized by Dispase treatment and floated in tissue culture medium (original x4). Such specimens have potential for use in tissue grafting procedures during reconstructive surgery.

desmosomes. Such cells therefore resemble normal squamous epithelial cells derived from skin and the oral mucosa. The only apparent difference between normal and metaplastic squamous epithelial cells is that treatment of metaplastic squamous cells with TGF-β in 0.1 mmol/L Ca^{++} preferentially induces terminal differentiation rather than reversible growth arrest.[36] This suggests that metaplastic squamous cells differ only minimally from normal squamous cells. In contrast, squamous carcinoma cells show numerous abnormalities in their ability to regulate the integrated control of proliferation and differentiation. For example, most carcinoma cells express defects in their ability to irreversibly growth-arrest and/or terminally differentiate.[38]

In conclusion, mucosal squamous cells of the oral cavity, oropharynx, and hypopharynx grow well in complete MCDB 153 and demonstrate proliferation and differentiation control mechanisms similar to those of epidermal keratinocytes. This cell culture system therefore should allow further investigation into the pathophysiology of human squamous mucosal cells and should facilitate the further development of these cells as a potential source of transplantable squamous mucosa for autogenous grafting.

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PREDICTIVE VALUE OF THE GLASGOW COMA SCALE FOR TRACHEOTOMY IN HEAD-INJURED PATIENTS

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Patients with severe head trauma often require prolonged intubation and subsequent tracheotomy. The Glasgow Coma Scale (GCS), an indicator of the severity of head injury, may help identify that subpopulation of trauma victims who will ultimately undergo tracheotomy. This retrospective study demonstrates through discriminant analysis that the likelihood of tracheotomy is significantly greater in patients with a GCS rating ≤ 7 than it is in patients with a GCS rating >7 ($p = .0001$). Conversely, the presence of thoracoabdominal or maxillofacial injury is associated with but not predictive of eventual tracheotomy. In the hope of minimizing complications and enhancing the utilization of hospital resources, this study argues for early tracheotomy in patients with a GCS score ≤ 7 who do not undergo craniotomy and are otherwise stable.

KEY WORDS — coma, head injuries, tracheotomy.

INTRODUCTION

In order to ensure airway patency, prevent aspiration pneumonia, and manage intracranial hypertension, victims of severe head trauma frequently require endotracheal intubation. Length of intubation is determined by the severity of head injury and the rapidity of patient recovery. As the potential for complications increases with protracted intubation, many trauma victims eventually require tracheotomy. The optimal time for conversion of an endotracheal tube to tracheotomy is controversial, and it is dependent upon the surgeon's assessment of the relative risks of intubation weighed against those of tracheotomy.

Since its introduction in 1974, the Glasgow Coma Scale (GCS) has been integrated into the initial assessment protocols for the neurologic evaluation of head-injured patients. Patient consciousness is assessed and summarized by the GCS rating, which is based upon three separate stimulated responses (Table 1).[1] The GCS rating has also been used to predict the neurologic outcome for those with head injury.[2]

Given that many patients with severe head injury ultimately undergo tracheotomy, we set out to determine if the GCS could help predict which of these trauma victims would receive tracheotomy. This study was designed to test the hypothesis that patients with a GCS rating ≤ 7 will ultimately undergo tracheotomy. The observations that severely head-injured patients often require prolonged artificial airway management and that complications of endotracheal intubation are related to protracted intubation were the impetus for this study.

METHODS AND MATERIALS

The charts of all head-injured patients who were admitted to Albany Medical Center (AMC) between March 1986 and July 1988 were reviewed. To be included in this study, patients had to meet the following criteria: 1) admission to AMC within 12 hours of injury, 2) GCS rating ≤ 12 within 24 hours of admission, 3) age between 15 and 55, 4) no prior history of head trauma or intracranial surgery, and 5) intubation or tracheotomy for airway control within 24 hours of hospitalization.

TABLE 1. GLASGOW COMA SCALE

	Score
Best motor response	
Obeys; moves limb to command and pain not required	6
Localizes; changing location of pain stimulus causes limb to follow	5
Withdraws; pulls away from painful stimulus	4
Abnormal flexion	3
Extensor response	2
No movement	1
Best verbal response	
Oriented; knows name, age, etc	5
Confused conversation; still answers questions	4
Inappropriate words; speech either exclamatory or at random	3
Incomprehensible sounds; do not confuse with airway obstruction	2
None; make note if intubation prevents speech	1
Eye opening response	
Spontaneous; already open with blinking (normal)	4
To speech; not necessarily to request eye opening	3
To pain; stimulus should not be to face	2
None; make note if eyes swollen shut	1

Total sum of motor + verbal + eye = GCS. Total can range from 3 to 15. (Adapted from Teasdale and Jennett.[1])

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TABLE 2. MECHANISMS OF INJURY

	No. of Patients
Motor vehicle accident	26
Pedestrian versus motor vehicle	5
Fall	5
Skiing accident	4
Assault	3
Industrial accident	3
Gunshot	1
Total	47

Computerized discriminant analysis[3] was used to identify which factors (ie, patient age, maxillofacial trauma, significant thoracoabdominal injury, closed or open head injury, focal or diffuse intracranial damage by computed tomographic scan, neurosurgical intervention, and GCS rating) could predict eventual tracheotomy. Patients were considered to have significant thoracoabdominal injury if they carried one of the following diagnoses: massive lung contusion, flail chest, multiple rib fractures (more than five ribs), massive splenic/liver lacerations, pancreatic leak, pelvic fracture, or spinal fracture.

Other variables evaluated include the mean length of intensive care unit (ICU) stay, mean length of intubation, and mean length of intracranial pressure (ICP) monitoring. Mechanisms of injury, length of mechanical ventilation after tracheotomy, and length of tracheotomy were also assessed. Tracheotomy was performed on the basis of a continuing need for artificial airway support and the judgment that the risk of continued intubation outweighed that of tracheotomy. All patients underwent tracheotomy for one or more of the following reasons: 1) prolonged mechanical ventilation, 2) management of secretions for the prevention of aspiration, and 3) to ensure airway patency.

RESULTS

Forty-seven patients met all the criteria for inclusion into this study; 65% were male and 35% were female. Their ages ranged between 15 and 51 years with an average age of 26. A variety of mechanisms of injury were represented by this population, but by far the most common was motor vehicle accidents (Table 2).

The mean length of ICU stay for all patients was 17.6 days, while their average length of intubation was 8.4 days. For those not undergoing tracheotomy, the average length of intubation was 7.6 days, while it was 9.5 days for patients who underwent tracheotomy after 24 hours of hospitalization. Three patients died, all with GCS scores below 7, and two died within 1 week of hospitalization. None of these received tracheotomy.

Subjects were divided into two groups based upon their GCS rating. Thirty-four patients had a GCS rating ≤ 7, and 13 patients in this study had a GCS rating >7. In each group, the male/female ratio and the average age reflected the group as a whole. The average length of ICU stay was 20.6 days for patients with a GCS score ≤ 7 and 10.0 days for patients with less severe head injury. As expected, patients with GCS scores ≤ 7 also had a longer average period of ICP monitoring than those with less severe trauma (5.6 versus 1.2 days). For patients with a GCS score ≤ 7, the mean number of days of intubation was 10, while it was 6.5 for less traumatized patients.

Twenty-eight patients in this study had a tracheotomy. Two had the procedure performed emergently at the time of admission. In 16 of the 28 patients, mechanical ventilation was required for 7 or more days after the tracheotomy was performed. All of these patients were either discharged with tracheotomy tubes in place or required more than 2 months of artificial airway management. Forty-two percent or 12 of the 28 patients required less than 1 week of mechanical ventilation after tracheotomy was performed. Eight of these 12 patients were discharged with the trachea cannulated in order to manage secretions and/or prevent aspirations. Three patients in this group of 12 required a minimum of 39 days of artificial airway management. One of the 12 patients required 14 days of endotracheal intubation, followed by 14 days of tracheotomy for airway maintenance, management of secretions, and prevention of aspirations. Therefore, the earliest decannulation in any patient with tracheotomy was 28 days after the time of injury.

To determine whether any group of the independent descriptor variables for the 47 patients could accurately predict which patients would eventually undergo tracheotomy, several discriminant analyses were performed. This technique calculates linear combinations of the independent predictor variables for the correct classification of each patient.[3]

Discriminant analysis of the entire patient group was able to predict correctly 85.1% of the time which patients would and would not undergo tracheotomy when GCS was used as the sole predictor variable ($p = .0001$). The predictive accuracy of this analysis did not increase after addition of other independent predictor variables such as age, maxillofacial trauma, thoracoabdominal injury, type of head injury (open versus closed; diffuse versus focal), or neurosurgical intervention. Three of these other variables were shown to be statistically related to the prediction of tracheotomy. In decreasing order of importance, they are neurosurgical intervention, thoracoabdominal injury, and the type of head trauma. However, including these variables in the discriminant analysis model did not improve the accuracy of the predictions.

On reexamining the patient population more carefully, the predictive value of the GCS is even greater. Seven of the 34 patients with a GCS rating

≤7 did not require tracheotomy. Of these, four had prompt neurosurgical intervention, two died within 1 week of admission, and one had an improved GCS at 72 hours. Of the patients who had craniotomy, only 60% (8/13) had tracheotomy, and 2 of the 13 died (one within 1 week of admission as noted above).

When the discriminant analysis was repeated with the same variables after exclusion of all patients who underwent craniotomy and those who died within 7 days of hospitalization, the GCS score could correctly predict tracheotomy 93.9% of the time ($p < .0001$). This analysis showed that thoracoabdominal trauma was the only other significant predictor variable. Thirty-three patients remained in this analysis, and 95% of the patients (19/20) with a GCS score ≤7 required tracheotomy. The patient who did not require tracheotomy in this group had an improved GCS rating of 8, 72 hours after injury. Of the subjects with a GCS score >7, 95% (12/13) did not require tracheotomy.

DISCUSSION

There is continued controversy over when to intervene with tracheotomy in patients who are intubated via endotracheal tube.[4-6] In 1981, Stauffer et al[4] reported that some patients could tolerate up to 3 weeks of intubation without suffering significant adverse sequelae. In 1984, Whited[7] presented prospective data that indicated that intubation beyond 10 days carries significant risk for severe injury to the larynx. Deutschmann et al[8] found a 25% incidence of paranasal sinusitis in 43 neurosurgical patients who were nasotracheally intubated and were not trauma victims. The mean length of intubation prior to the diagnosis of paranasal sinusitis was 7.5 days in this patient group. In 1988, Astrachan et al[9] asked critical care nurses to compare prolonged intubation with tracheotomy. The overwhelming majority of nurses believed that tracheotomy was superior to prolonged endotracheal intubation (>10 days) with regard to patient comfort, ease of swallowing, management of oral secretions, ease of suctioning, ease of mouth care, and ease of communication. Their patient population had a 57% early complication rate associated with intubation. These researchers urge early tracheotomy for patients who need prolonged respiratory support.

It is the goal of this analysis to predict which patients ultimately will receive tracheotomy so that it can be performed prior to the appearance of complications. As patients remain comatose, their need for continued airway protection and prevention of aspiration persists. This is the link between the neurologic outcome and tracheotomy. A study by Jennett et al[2] showed that 54% of patients with a GCS score between 5 and 7 were vegetative or dead 6 months after injury and that 80% of the patients with worse scores did just as poorly.

The utility of the GCS remains well tested in time, but it does have limitations.[2,10,11] Subjects can be incorrectly categorized by any factor that would artificially lower their GCS score. Therefore, prior to use of the GCS to predict neurologic outcome, all head-injured patients should be resuscitated from hypoxia and hypoperfusion as well as recovered from illicit drugs or alcohol.

In combination with one another, the three separate stimulated responses elicited by the GCS (best eye opening, best verbal, and best motor responses) are reliable. Abnormal responses have the potential for predicting poor outcome. Independently, each of these stimulated responses has shortcomings that limit the power of the GCS to prognosticate an outcome.

For example, the eye opening response is rendered uninformative by the presence of bilateral severe periorbital edema that would conceal a patient's ability to respond to stimulus. Its reliability is further hampered by a time constraint of 72 hours. This is because patients who are known to be deeply comatose have been observed with spontaneous eye opening as early as 72 hours after a neurologic insult.

Neither the verbal nor motor responses are limited by any time constraint. In fact, the return of the verbal response long after its initial absence often heralds the end of coma.[9] On the other hand, the GCS score assigned to patients for their verbal response can be inaccurate because the patient either is intubated or has significant oromandibular trauma.

Of the stimulated responses assessed during the GCS rating, the best motor response is the single most prognostic element.[9] Its rating can be affected by either massive orthopedic injury or spinal cord damage. The adverse significance of an abnormal motor response is greatest when it is seen in conjunction with diffuse intracranial injury. Becker et al[10,11] have shown that the best motor response score is less reliable as a prognosticator when focal intracranial injury is present that is amenable to repair through craniotomy (eg, depressed skull fractures, epidural and subdural hematomas). In other words, it is difficult to predict the neurologic outcome in trauma victims who undergo craniotomy.[10,11] This is also supported by data from our study.

This investigation attempts to control some of the potential limitations inherent to the GCS and to a retrospective study. There are many more patients in this evaluation with severe head trauma than there are those with a GCS score >7 (ie, 34 versus 13 patients). This is readily explained by the criteria for entrance into our study. Since patients were selected for analysis on the basis of an artificially controlled airway and because not all patients with GCS ratings >7 always require intubation, there are many more subjects with severe head injury entered into this study. This aspect, however, helps to keep the GCS scores meaningful and prevents disparity. Otherwise, in a given patient, the GCS score might actually be higher if he or she were not intubated. This is particularly important in defining a cutoff point in predicting tracheotomy.

One drawback of this study is that GCS scores were not available on each patient daily through the first 72 hours of hospitalization. A repeated GCS score at 72 hours would ensure more time for patient stabilization and for the elimination of any illicit drugs or alcohol used prior to head injury. In fact, the only patient who was incorrectly predicted to undergo tracheotomy was improved at 72 hours, with a GCS score of 8. A repeated GCS rating at 72 hours would have precluded that incorrect prediction of tracheotomy.

Our initial hypothesis is supported by statistical analysis, and our results show that in this select patient population, the GCS is predictive for tracheotomy as an outcome. The data also indicate that neurosurgical intervention, the type of intracranial injury, and concurrent thoracoabdominal injury are correlated with eventual tracheotomy.

Although on the basis of this study we cannot recommend rigid criteria for the timing of tracheotomy in severely head-injured patients, we can recommend that unless clinically indicated by trauma, tracheotomy should not be performed on the basis of GCS rating prior to the third day of hospitalization. This recommendation will help prevent unnecessary tracheotomy.

This study shows that patients with severe head injury (GCS ≤ 7) who do not undergo neurosurgical intervention and have diffuse intracranial injury will ultimately require a minimum of 28 days of artificially controlled airway. Since there is a wide body of evidence in the literature that documents the appearance of significant complications from endotracheal intubation between 7 and 10 days, it seems prudent to recommend tracheotomy for those trauma victims who fulfill the above criteria and have been intubated for 7 or more days. This could reduce intubation-related complications, facilitate nursing care, decrease ICU hospitalization, and perhaps diminish overall costs.

CONCLUSIONS

1. Patients who sustain diffuse intracranial injury, do not undergo operative neurosurgical intervention, and have a GCS rating ≤ 7 often require prolonged intubation and subsequent tracheotomy (95%).
2. Consideration for early tracheotomy is advocated on the basis of the results of our analysis.
3. Tracheotomy on the basis of the GCS rating is not recommended prior to 3 days of hospitalization unless otherwise clinically indicated.
4. Prospective study to further assess airway management in the head-injured patient is indicated.

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HISTOLOGY OF ISSHIKI THYROPLASTY TYPE I

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Isshiki thyroplasty type I, an open surgical procedure to medialize the true vocal cord, has been proposed as an alternative to Teflon injection in selected cases of recurrent nerve paralysis or vocalis muscle atrophy. This operation was performed in a man with a mediastinal tumor and a paralyzed vocal cord in an intermediate position. He died 1 month later, and his larynx and recurrent nerve were studied histologically. The gross and microscopic changes in the larynx caused by this operation are discussed, and the pathologic changes in the recurrent nerve leading to the paralysis are examined.

KEY WORDS — aspiration, laryngeal pathology, recurrent nerve, thyroplasty, vocal cord paralysis.

INTRODUCTION

The concept of medializing a paralyzed vocal cord by inward displacement of an overlying segment of thyroid cartilage was advocated by Payr[1] at the beginning of the century. Others have continued to modify and refine this operation,[2-9] despite the popularity of Teflon injection for vocal rehabilitation.[10] Dissatisfaction with the ability of Teflon injection to close large glottic gaps and to treat bowed, atrophic cords,[8] as well as its permanent nature and tendency to induce fibrous reaction, has inspired surgeons to look for alternate procedures.

In 1974 Isshiki et al[5] outlined a series of laryngeal framework operations designed to alter the mass, tension, and position of the vocal cords to change voice quality. The first of these phonosurgical procedures, thyroplasty type I, medially displaces the cord by depressing a rectangular window of thyroid cartilage that is secured with a piece of autologous cartilage, or in the modification proposed by Koufman,[7] by a custom-fitted block of siliconized rubber (Silastic) (Fig 1). By adjusting the thickness and position of the block, vocal cord position can be fine-tuned intraoperatively. The locally anesthetized patient phonates as the block is moved to produce the best voice quality.

Despite several animal studies and numerous reports of success with this technique in patients, there is a paucity of information about the histologic effects of thyroplasty on the human larynx. We present the anatomic findings in the larynx of a man who died 1 month after Isshiki thyroplasty type I.

CASE REPORT

The patient was a 71-year-old man with a 1-year history of prostate carcinoma metastatic to bone. He was treated with a transurethral resection of the prostate and local irradiation of the pelvis and spine. He presented 5 months later with evidence of metastases to mediastinal lymph nodes and a 2-week history of progressive hoarseness.

At otolaryngologic examination he was alert and in no respiratory distress, but was weak and complained of back pain. He spoke only in a whisper and complained that he could not communicate with his wife, who had a hearing loss. Indirect laryngoscopy revealed a bowed, paralyzed left vocal cord in an intermediate position. Voice quality improved with compression of the left thyroid ala.

Although he had both marginally compensated cardiac disease and metastatic prostate cancer, the

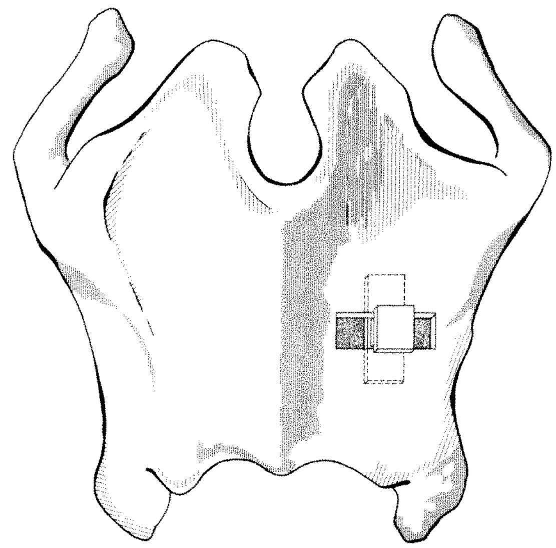

Fig 1. Window of thyroid cartilage, depressed and held in place by Silastic block.

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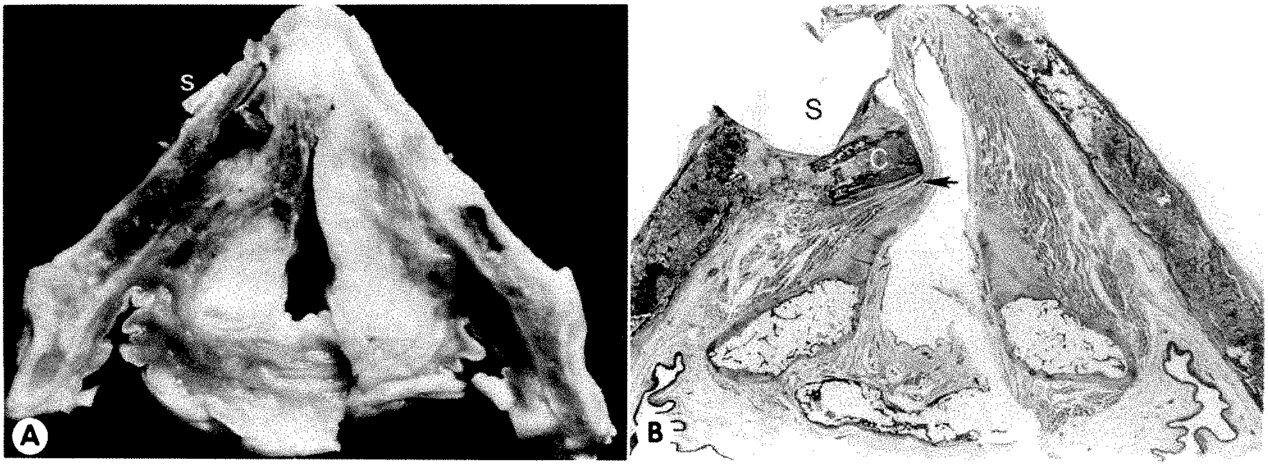

Fig 2. Horizontal sections. A) Gross section just above true cord level. Silastic block (S) has medialized cord to near-midline position. B) Histologic section at level of true cords. S — dissolved Silastic block, C — depressed thyroid cartilage, arrow — atrophic true vocal cord.

patient was eager to be able to communicate again. After discussion with his internists, it was agreed that he could tolerate a short procedure under local anesthesia. As he had a bowed cord and a large glottic chink and there was hope that his mediastinal disease might respond to radiation therapy with subsequent return of vocal cord function, an Isshiki thyroplasty type I was selected.

The operation took approximately 1 hour to perform. It was made more difficult by extensive calcification of the thyroid cartilage and the patient's inability to hold still in a supine position because of back pain.

In the immediate postoperative period, the patient had a strong voice with an 8-second phonation time and could talk with his wife again. His cardiac problems persisted, however, and on the sixth postoperative day he developed congestive heart failure. His pulmonary status worsened, and he suffered a respiratory arrest and died 1 month following the thyroplasty. He was not endotracheally intubated or tracheotomized.

At autopsy he was found, unexpectedly, to have a small cell carcinoma of the left lung with metastases to bone, liver, and lymph nodes, as well as extensive atherosclerotic cardiovascular disease.

LARYNGEAL PATHOLOGY

On gross examination, the left vocal cord was thinned and atrophic. It was closely approximated to the contralateral cord anteriorly, but a posterior gap remained (Fig 2A). The Silastic block used to medialize the segment of thyroid cartilage was covered laterally by dense connective tissue. There was no intralaryngeal hemorrhage or vocal cord granuloma.

The left recurrent laryngeal nerve was traced to the mediastinum, where it was encased in tumor mass near the aortic arch (Fig 3).

The larynx was formalin-fixed, decalcified, and whole-mounted in paraffin. Serial horizontal sections at 20-μm intervals were cut at the glottic level and in the area of the cricothyroid joint. Segments of the left recurrent nerve were examined in the region of the cricothyroid joint and in the mediastinum. The laryngeal sections were stained with hematoxylin and eosin, and the recurrent nerve sections were examined after Luxol fast blue staining for myelin and Bodian staining for axons. The recurrent nerve of an age-matched patient was studied by semiquantitative light microscopy for comparison.

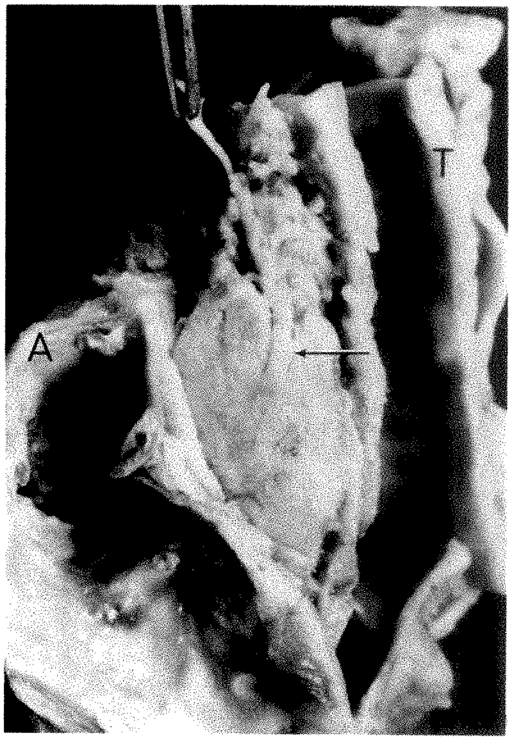

Fig 3. Recurrent nerve (arrow) encased in tumor. T — tracheal wall, A — aortic arch.

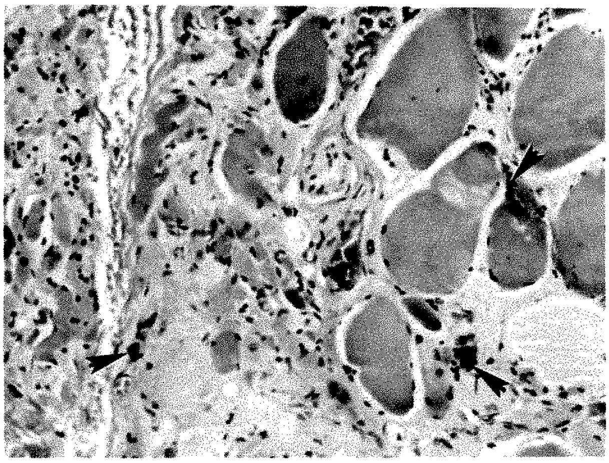

Fig 4. Vocalis muscle with neurogenic atrophy and fibrosis (H & E, original x175). Fibers that are most atrophic are arranged in groups with clumps of hyperchromatic nuclei (arrowheads).

A whole-mounted section at the level of the true cords demonstrated remarkable atrophy of the vocalis muscle (Fig 2B). The Silastic block dissolved during preparation, but its impression was clear. It was surrounded by a thin fibrous capsule and showed no evidence of migration or extrusion into the laryngeal lumen. The depressed cartilage segment had pivoted on its perichondrium and showed greater anterior than posterior displacement.

At higher magnification there was little hemosiderin deposition or inflammatory response at the surgical site. The vocalis muscle showed evidence of neurogenic atrophy with disparity in the size and shape of individual fibers, and an increased number of sarcolemmal nuclei. The most atrophic muscle fibers were arranged in groups, associated with clumps of hyperchromatic nuclei (Fig 4). Fatty infiltration and fibrosis of the interstitium suggested chronic, progressive denervation. The thyroid cartilage had ossified, and its marrow cavity was partially replaced by metastatic small cell carcinoma.

The recurrent laryngeal nerve was examined within the tumor mass and at the level of the cricothyroid joint. The mediastinal segment was encased in tumor with infiltration of the perineurium of some fascicles by small, dark tumor cells (Fig 5A). Individual nerve fascicles were splayed and compressed, but their endoneurium was intact. Luxol fast blue staining for myelin showed nearly complete loss of myelin sheaths, but Bodian staining confirmed the presence of intact axons without evidence of wallerian degeneration. Distal to the tumor there was partial restoration of myelin (Fig 5B).

DISCUSSION

Examination of this larynx confirms several of the findings in the canine model of thyroplasty.[9] Medial displacement of a segment of the thyroid cartilage causes a corresponding medialization of the anterior portion of the vocal cord without impinging upon the airway. This same lack of effect upon the posterior glottis may, in part, account for the mixed success of thyroplasty in controlling aspiration. Isshiki et al[11] proposed an arytenoid adduction procedure to be used when the posterior glottic chink is very wide or the cords are at different levels.

There is no evidence of intralaryngeal hemorrhage or scarring of the vocal cord when dissection is kept lateral to the inner perichondrium of the thyroid cartilage. The lack of scarring around the Silastic implant suggests that the operation may be reversible if the implant is removed, at least within 1 month.

The depressed cartilage island derives its blood supply from the inner perichondrium, yet this is sufficient to support not only the chondrocytes but also the metabolically active marrow of the ossified portion of the cartilage.

Groups of muscle fibers were at various stages of degeneration at the time of the patient's death.

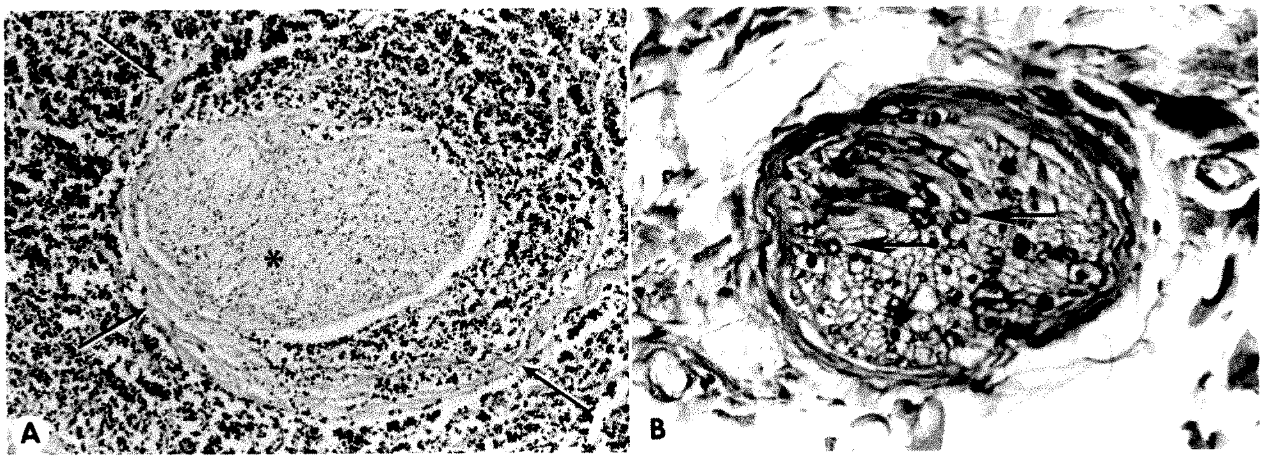

Fig 5. Recurrent laryngeal nerve (Luxol fast blue, original x97). A) Fascicle (asterisk) encased in tumor cells with invasion of perineurium (arrows). There is near-total demyelination of axons. B) Nerve at level of cricothyroid joint with few remaining myelinated axons (arrows).

Changes ranging from minimal atrophy to complete degeneration with fibrosis suggest that the atrophy was neurogenic and of several months' duration. This is interesting, because the patient's hoarseness started just 2 weeks prior to the operation. It is possible that the vocalis muscle is capable of compensating for progressive neuronal loss to a critical point and then paralysis and hoarseness ensue.

The recurrent nerve shows compression and splaying of fascicles by the mediastinal tumor. Demyelination is focal; it is almost complete in the mediastinal segment, with reconstitution of some myelin sheaths at the level of the larynx. With such complete segmental demyelination, the nerve certainly could not have provided functional motor impulses to the larynx. Still, as the axons remained intact, there would have been a chance of laryngeal reinnervation if the tumor had regressed with therapy.

Following recurrent nerve section, a paralyzed vocal cord typically assumes a paramedian position because of the unopposed adducting action of the cricothyroid muscle, innervated by the superior laryngeal nerve.[12] That the vocal cord was instead seen preoperatively to be in an intermediate position in this case is consistent with previous cases in which the recurrent nerve was affected by a tumor or aneurysm in the mediastinum.[13] Fukuda and Kirchner[13] demonstrated that this was the result of compression of ascending vagal afferents carrying pulmonary stretch receptor information. These afferents are involved in the reflex arc that stimulates cricothyroid muscle contraction during deep inspiration. Stretching or compressing the vagus nerve in the mediastinum after recurrent nerve section results in a reversible deviation of the cord from a paramedian to an intermediate position in the dog model.[13,14] Unfortunately, such a mechanism cannot be definitively proven in this case, as the vagus nerve was not available for study.

Management of the paralyzed vocal cord remains a challenge. Until complete surgical reinnervation of the laryngeal musculature is accomplished, operations to medialize the weakened vocal cord, increase its bulk, improve its tone, and narrow the posterior glottic chink will continue to be proposed. A simple design, potential for reversal, and an adjustable extent of medialization should be features of operations to restore voice in this setting. In addition, since many patients with paralyzed vocal cords are very ill with chronic aspiration or advanced cancer, the operation should be short in duration, be performed with the patient under local anesthesia, and require the minimum of patient cooperation.

Clinical experience and histologic evidence support Isshiki thyroplasty type I as an excellent alternative to Teflon injection in the management of the paralyzed vocal cord.

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LASER EXCISION OF EARLY VOCAL CORD CARCINOMA: INDICATIONS, LIMITATIONS, AND PRECAUTIONS

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Forty-six patients referred for laser surgery of early vocal cord carcinoma were treated by laser excisional techniques with or without radiotherapy. Mean follow-up was 3.5 years. There was a 90% rate of carcinoma control (18 of 20 patients) in patients with untreated mid-vocal cord T1 carcinomas without involvement of the anterior commissure or vocal process or deep muscle invasion. Larger, more invasive T1 vocal cord tumors (13 patients) had laser excision followed by radiotherapy without recurrence. Careful patient selection and accurate histopathologic evaluation are key elements for successful treatment.

KEY WORDS — carbon dioxide laser, endoscopic cordectomy, endoscopic tumor staging, excisional biopsy, laser cytoreduction.

INTRODUCTION

Endoscopic treatment of early vocal cord carcinoma is not a new concept, having originated before the development of laser technology.[1,2] Early detection of vocal cord carcinoma, facilitated by office laryngoscopy with fiberoptic telescopes and flexible instrumentation in addition to sparse true vocal cord lymphatics, makes this a highly curable tumor in its early stage. Although radiotherapy is still considered the treatment of choice in many medical centers, the concept of laser excisional biopsy has gained gradual acceptance since its introduction by Strong and Jako in 1972.[3]

The advantages of laser excisional biopsy as a treatment for T1 vocal cord carcinoma, as opposed to radiotherapy, are well known. These advantages include a one-session therapy with an endoscopic approach, less morbidity and fewer side effects, and cost-effectiveness when compared with 6 weeks of radiotherapy. Our policy has been to save radiotherapy when possible for more threatening potential second primary carcinomas that may develop in the head and neck region.

When the clinician adheres to careful patient selection for laser excisional biopsy, excellent control rates have been reported. Control rates in the range of 89% to 96% have been reported by Blakeslee et al,[4] Ossoff et al,[5] Koufman,[6] and Wetmore et al.[7] These control rates are certainly more than acceptable when compared with the "gold standard," radiotherapy. Advocates agree that the criteria for use of endoscopic laser treatment are the ability to expose the larynx with a large-lumen laryngoscope and a mid-vocal cord tumor with no involvement of the anterior commissure, vocal process, ventricle, or subglottic larynx. Patients treated in this fashion should also have acceptable medical risks for general anesthesia.

As with any new therapeutic modality, however, overenthusiastic use may occur. Endoscopic laser excision is so appealing to patients that they often pressure the laryngologist into extending the indications for treatment. It is certainly tempting to extend the vocal cord resection to the anterior commissure or perhaps to "chase" the tumor margins deep into the vocalis muscle up to the thyroid cartilage perichondrium. These extensive resections of T1 vocal cord carcinomas have been justified by frozen section margins and random biopsy specimens taken from the deep margins of resection. An increased recurrence rate has been noted by Krespi and Meltzer[8] when laser surgery has been extended to anterior commissure tumors. All five patients treated in their series had recurrent disease 3 months to 1 year after laser excision. Three of the four recurrences noted in the series of Wetmore et al[7] also involved the anterior portion of the true vocal cord, including the anterior commissure.

This paper presents our series of 46 patients with early (T1 and T2) vocal cord carcinoma specifically referred for laser treatment. These patients were treated with the carbon dioxide laser for cure and in some instances for staging purposes. This paper will stress patient selection and the limitations of this approach when treating patients with early vocal cord carcinoma.

MATERIALS AND METHODS

Our technique for laser excisional biopsy is essentially similar to that reported by Blakeslee et al[4] and will not be the emphasis of this paper. In summary, a large-bore type of laryngoscope of the Dedo-Jako

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LASER TREATMENT OF EARLY VOCAL CORD CARCINOMA (N = 46)

Type of Tumor	*Therapeutic History*	*No. of Patients*	*Tumors Controlled*	
			No.	*%*
Small T1	No previous therapy	20	18	90
Small T1	Radiotherapy	5	5	100
Large T1	Laser and radiotherapy	13	13	100
T2	Laser and radiotherapy	7	5	71
T2	Laser and partial laryngectomy	1	1	

Follow-up ranged from 2 to 6 years.

design (Pilling Company, Philadelphia) was used for exposure and the Boston University suspension apparatus for positioning (Pilling Company). Before the excisional biopsy, supravital staining with 2% toluidine blue was used routinely to detect the surface extent of the carcinoma.[9] This staining was also useful for determining multicentric mucosal lesions. Intraoperative steroids (dexamethasone), 0.15 mg/kg body weight, were administered intravenously before induction of anesthesia to minimize any perioperative edema that might occur secondary to the procedure.

The biopsy excision was performed by grasping of the tumor with an up-biting cup forceps and its placement under traction in a medial direction. Care was taken to include at least a 2- to 3-mm margin around the tumor by use of a technique described by Blakeslee et al.[4] Most often the CO_2 laser was used in an intermittent pulse setting so as to avoid heat coagulation of the specimen. The orientation of the surgical specimen for pathologic frozen section margin control is most important. The specimen was placed on a Telfa or cardboard sheeting and tacked in place with small pins. The specimen was oriented to the pathologist, and under the guidance of the clinician, multiple sections along the long axis were made. All frozen section margins were reviewed carefully with the pathologist. Free surgical margins must be obtained on frozen section analysis because permanent sections are often hard to orient. No attempt was made to sample the deep surgical bed because this would have resulted in random biopsy specimens. If the margins of the frozen section were involved or were too close for safety, a deeper excisional margin was obtained with the surgical laser.

Patients were followed up carefully in the usual fashion for patients with head and neck carcinoma. Office laryngoscopy was performed with either a flexible fiberoptic laryngoscope or a rigid 90° rod lens telescope or both.

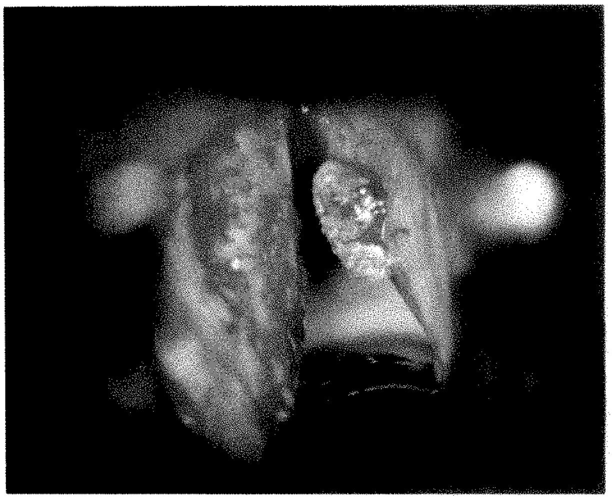

Fig 1. Endoscopic photograph of exophytic polypoid squamous cell carcinoma of right vocal cord. This patient was ideal candidate for laser excisional technique because patient had undergone radiotherapy for left vocal cord tumor 5 years earlier.

PATIENTS

Forty-six patients referred for laser surgery of early vocal cord carcinoma were treated at the Lahey Clinic Medical Center from 1982 to 1987 (see Table and Figs 1 and 2). Patients with carcinoma in situ or dysplasia were excluded from this study. Follow-up varied from 2 to 6 years, with a mean of 3.5 years. Twenty-five patients with small T1 vocal cord carcinomas were treated with endoscopic laser excisional techniques. Twenty of these patients had not been treated previously, and five patients had a history of previous radiotherapy (2 to 6 years before referral). This latter group most probably had second primary carcinomas in the same region staged as a T1 vocal cord cancer. All patients met the criteria for laser excision, namely, a mid-vocal cord lesion, an easily exposed larynx, good risk for general anesthesia, and no involvement of the anterior commissure, subglottic larynx, ventricle, or vocal process.

Thirteen patients were treated by endoscopic laser excisional biopsy for larger T1 vocal cord carcinomas. These patients were found to have invasive squamous cell carcinoma into the vocalis muscle but without limitation of mobility. Although these patients were still clinically classified as having T1 vocal cord carcinoma, they were considered "biologically" to have T3 carcinoma because of deep vocalis muscle invasion. Complete tumor removal in these patients would have meant a subtotal vocal cordectomy. Rather than chasing these lesions with the CO_2 laser by multiple excisions and frozen section clearance control, we chose radiotherapy as the definitive therapy, with minimal delay between laser excision and radiotherapy. The anterior commissure was involved in nine of these patients and the full length of the cord in three patients; one patient had bilateral mid-vocal cord invasive carcinoma.

Eight patients with T2 vocal cord carcinoma were referred for laser therapy. The CO_2 laser was used in these patients to stage these tumors accu-

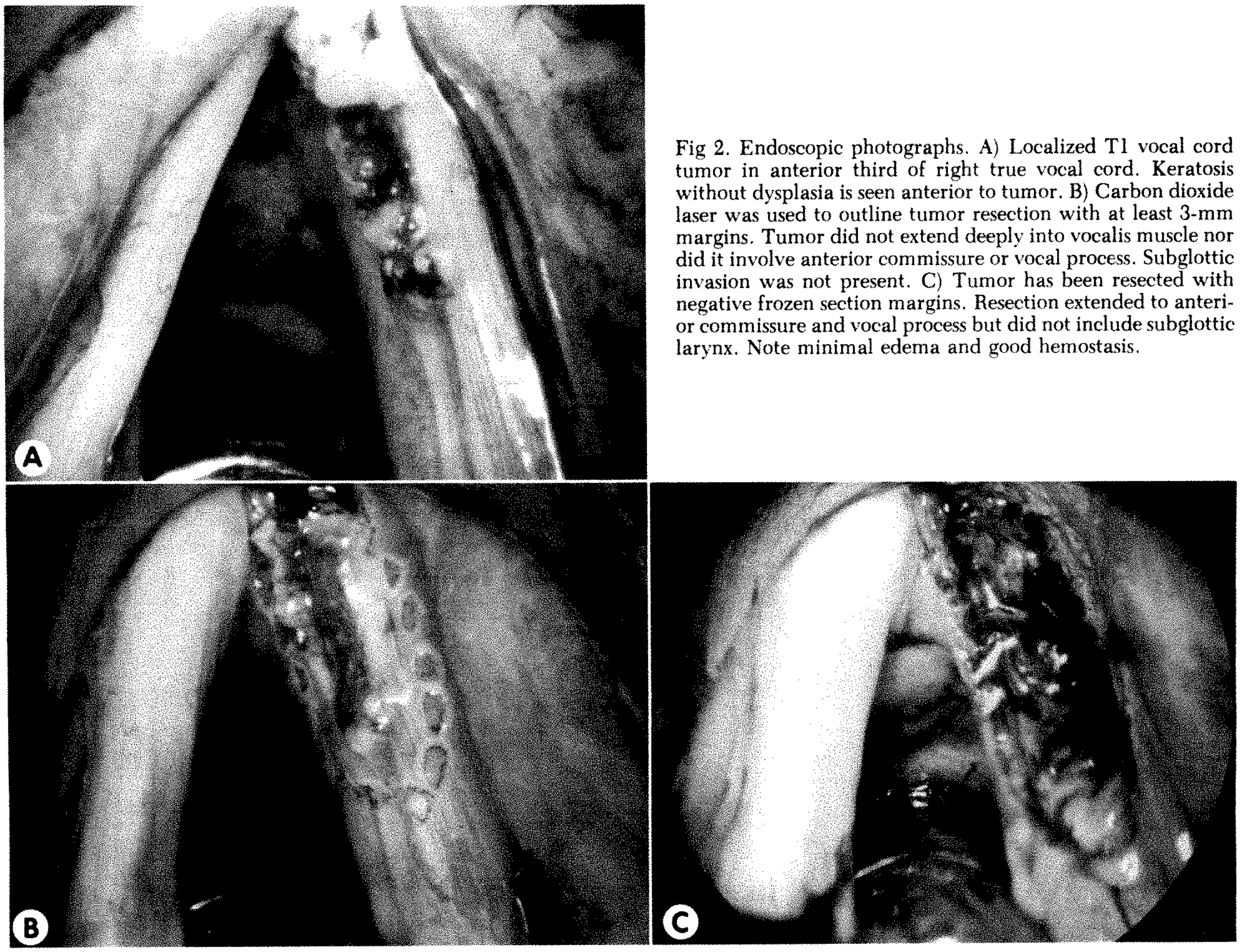

Fig 2. Endoscopic photographs. A) Localized T1 vocal cord tumor in anterior third of right true vocal cord. Keratosis without dysplasia is seen anterior to tumor. B) Carbon dioxide laser was used to outline tumor resection with at least 3-mm margins. Tumor did not extend deeply into vocalis muscle nor did it involve anterior commissure or vocal process. Subglottic invasion was not present. C) Tumor has been resected with negative frozen section margins. Resection extended to anterior commissure and vocal process but did not include subglottic larynx. Note minimal edema and good hemostasis.

rately by excisional biopsy and to reduce the tumor bulk. Deep extension into the vocalis muscle, ventricle, or subglottic larynx was noted. Seven of these patients went on to have radiotherapy, and one patient refused radiation therapy and underwent partial laryngectomy.

RESULTS

In the series of patients (20) with small untreated T1 vocal cord carcinoma (Table), the control rate was 18 of 20 patients (90%). All patients with a history of previous radiotherapy presenting with a probable second vocal cord primary carcinoma had their disease controlled by laser excisional therapy (five patients). Patients with larger, more invasive T1 vocal cord carcinoma underwent laser excision and radiotherapy, with complete control of their disease. There was no additional morbidity associated with radiotherapy after laser excisional biopsy.

Eight patients were referred with T2 vocal cord carcinoma for the express purpose of having laser therapy. These patients were advised that laryngoscopy was necessary to determine the tumor margins accurately before any decision regarding laser therapy was made. The laser was used in these patients as a staging device to excise the tumor subtotally, particularly the more bulky lesions, to determine the degree of extension accurately. After this accurate staging, seven patients had radiotherapy. Five of these patients did well, with no recurrence (71%). A total laryngectomy was done for salvage in two patients in whom radiation therapy failed. These patients are currently free of carcinoma. One patient refused radiotherapy after the laser staging procedure and went on to have a vertical partial laryngectomy and is now free of any tumor after 3 years.

None of the 46 patients in this series has persistent carcinoma on completion of their definitive therapies. No complications resulted from the use of the CO_2 laser. Specifically, there was no incidence of chondronecrosis or chondritis after either the laser or combined laser and radiation therapy.

DISCUSSION

Excellent control of early vocal cord carcinoma is possible with one endoscopic treatment. It is to be stressed, however, that this small vocal cord carcinoma should be in the middle portion of the vocal cord and have good exposure. Excisional biopsy has the advantage of providing a histologic specimen derived from a complete excision. These tumors should never be vaporized, with the clinician using histologic control from random deep biopsies. With this rationale for treatment, our plan is to save radiotherapy for those patients who are not good risks for general anesthesia and for patients with larger, more invasive T1 vocal cord carcinoma. With an incidence of second primary carcinoma in the head and neck as high as 20%, it is logical to reserve radiotherapy for a more threatening carcinoma of the head and neck.

Large vocal cord carcinomas in the T1 category, specifically those involving the anterior commissure or the vocal process, should be staged by subtotal excision and debulked with the CO2 laser. The anterior commissure is a particularly difficult area to control histologically by an excisional technique. Because there is no perichondrial barrier to prevent tumor extension into the cartilage, laser excision is fraught with danger. If deep extension into the cartilage is noted at the time of laser staging, an open partial laryngectomy, frontolateral type, or possibly total laryngectomy may be chosen for definitive treatment. Computed tomography of the larynx has not been helpful for the staging of cartilage invasion.

If deep vocalis muscle involvement is noted at the time of laser excision of larger T1 vocal cord carcinomas, further excision to the depths of the thyroid perichondrium is not advisable. Although tumor control may be possible in this situation, the functional result, ie, voice, is superior with radiotherapy rather than extensive cordectomy. If, however, vocal cord mobility is limited, as seen with larger T1 or T2 vocal cord carcinomas, better control can be obtained with open partial laryngectomy than with radiotherapy.

Patients are often referred after radiotherapy failure for a laser salvage procedure. Blakeslee et al[4] reported a 50% control rate for these patients. It is our experience as well that unless the vocal cord carcinoma persistent after radiotherapy is well localized as a surface recurrence, it is difficult to be sure of the excision margins. It is not uncommon to find nests of vocal cord carcinoma between areas of radiation fibrosis deep in the vocalis muscle. With this type of difficult histologic control, laser excision is often unsuccessful. If these patients are suitable candidates, open partial laryngectomy is the preferred procedure.

A major pitfall in the use of the laser for endoscopic therapy for vocal cord carcinoma is the difficulty of assessing frozen section and permanent section margins. This technique necessitates close cooperation between the clinician and the pathologist. It is extremely important to have a frozen section facility available in the operating room area. The clinician must hand-carry the specimen to the pathologist, orienting the tissue for multiple serial sections. If this specimen is allowed to contract and curl up on itself, an erroneous diagnosis can be made. The excised specimen is preferable for frozen section sampling rather than random deep biopsy specimens from the base of the excision. The latter technique may miss a focus of deep invasion. It is also a false sense of security that leads the physician to advise laser excision and close follow-up for a large invasive carcinoma. Routine follow-up by laryngoscopy may indicate a normal vocal cord surface with a focus of deep carcinoma not visible to the clinician. The first sign of recurrence may be a fixed vocal cord, necessitating partial or, most often, total laryngectomy. All patients in our series with large T1 vocal cord carcinomas were free of any tumor after radiotherapy.

The use of the laser as a cytoreduction and staging device before definitive therapy is certainly an attractive concept. Tumor debulking, however, as a treatment modality for carcinoma has not proved to be of any benefit over radiotherapy alone. The laser, however, permits accurate staging of the carcinoma when one is dealing with exophytic growth without impairment of vocal function. If the tumor growth pattern is primarily deeply infiltrative, then radiotherapy alone without "laser staging" is indicated.

Although carcinoma in situ and severe dysplasia are not subjects of this paper, they are treated with the CO2 laser in an excisional mode. Supravital staining using 2% toluidine blue permits the clinician to detect mucosal or surface extent and multicentricity. A small-spot CO2 laser (300 μm) with a microscope attachment permits accurate excision of the unhealthy mucosal surfaces. The depth of laser excision is to the superficial aspect of the vocalis muscle, with complete excision of the mucosal surface and the underlying submucosal space. Delicate microlaryngeal instruments are used for handling the specimen. A simple vocal cord stripping is not advised because microinvasion from carcinoma in situ is often difficult to detect. The pathologist requires a deeper full-thickness specimen, which is not usually provided by vocal cord stripping. Because multicentricity is common with carcinoma in situ, excision of the dysplastic areas is advised rather than radiotherapy. If carcinoma in situ becomes recurrent, a more aggressive excision is advised.

We have advised our patients to eat a diet rich in vitamin A. Although there is no evidence to show that vitamin A or retinoic acid will prevent the recurrence of carcinoma in situ, there is certainly good evidence to show that it may be of some benefit in general cancer prevention.[10]

In conclusion, excisional biopsy with the CO2 laser is a valid treatment for carefully selected patients with small invasive T1 vocal cord carcinomas. There is certainly nothing magical about the use of the CO2 laser, however, as opposed to other modalities, such as the cold knife, electrocautery, and cryoprobe. The laser provides a no-touch technology with microprecision and excellent hemostasis. It is important, however, not to overextend the indications of this extremely useful technology to larger tumors of the intrinsic larynx. Careful patient selection and accurate histopathologic evaluation are key elements for ultimate success.

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PAN AMERICAN ASSOCIATION OF OTORHINOLARYNGOLOGY–HEAD AND NECK SURGERY

The XXII Congress of the Pan American Association of Otorhinolaryngology–Head and Neck Surgery will be held November 23-27, 1990, in Catagena, Colombia. For further information, contact Pedro Blanco, President, Pan American Congress, Hospital Universitario del Valle, 3er Piso Servicio de Otorrinolaringologia, Cali, Colombia.

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IMPORTANCE OF IRON REPLETION IN THE MANAGEMENT OF PLUMMER-VINSON SYNDROME

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Plummer-Vinson syndrome (PVS) is characterized by iron deficiency anemia, upper esophageal stricture, cervical dysphagia, and glossitis. The precise role of iron deficiency in PVS has yet to be defined and remains a subject of much debate. A 29-year-old woman with PVS is presented. The patient had a 4-year history of severe iron deficiency anemia, a 2-year history of progressive dysphagia and weight loss, and a greater than 90% benign upper esophageal stricture. Iron therapy alone resolved her dysphagia and anemia, and a follow-up esophagram 1 year later showed a residual stenosis of less than 30%. The development of severe iron deficiency anemia in this patient 2 years before the onset of dysphagia, as well as the response of the stricture to iron repletion, supports the theory that iron deficiency can cause dysphagia and upper esophageal strictures. The occurrence of glossitis, gastritis, and esophagitis in iron deficiency demonstrates the adverse effects of iron depletion on the rapidly proliferating cells of the upper alimentary tract.

KEY WORDS — iron deficiency anemia, Paterson–Brown Kelly syndrome, Plummer-Vinson syndrome, sideropenic dysphagia, upper esophageal stricture and web.

INTRODUCTION

The association of iron deficiency anemia and upper esophageal webs was originally described by the laryngologists D. R. Paterson[1] and Brown Kelly,[2] then later by the gastroenterologists Plummer and Vinson.[3] This uncommon syndrome is most often seen in middle-aged women from the northern latitudes and is associated with hypothyroidism, autoantibodies, and hypopharyngeal carcinoma.[4-6] The following case report, which demonstrates the successful management of a patient with this syndrome by iron repletion alone, highlights the etiologic role of iron deficiency and the therapeutic importance of iron repletion in Plummer-Vinson syndrome (PVS). The medical literature is reviewed, and the etiology and management of PVS are discussed.

CASE REPORT

A 29-year-old woman presented to the head and neck surgery clinic with a 2-year history of progressive dysphagia with solids, odynophagia, a 9-kg weight loss, and a 4-week history of dysphagia with liquids. She described a feeling of soreness in her lower neck with deglutition; however, once the food bolus passed the sternal notch, the pain completely resolved. Four years before presentation, the patient was noted to have a severe microcytic, hypochromic anemia. She had not received previous treatment for her anemia. Her family history and additional medical history were unremarkable.

On examination, the patient had mild glossitis with atrophy of the filiform papillae (Fig 1), angular cheilitis, and slight spooning of the nails. Her white blood cell (WBC) count was 2,900 cells/mm^3 (normal range, 4,500 to 11,000) with a normal differential, hematocrit was 21.1% (normal range, 34.9% to 46.9%), platelet count was 418,000 cells/mm^3 (normal range, 150,000 to 440,000), mean corpuscular volume (MCV) was 59 fL (normal range, 88 to 110), reticulocyte count was 0.7 cells/mm^3, albumin was 4.7 g/dL (normal range, 3.2 to 5.0), serum iron was 23 μg/dL (normal range, 65 to 175), total iron binding capacity (TIBC) was 474 μg/dL (normal range, 250 to 410), ferritin was less than 10 ng/dL (normal range, 31 to 295), glucose-6-phosphate dehydrogenase activity was normal, and hemoglobin electrophoresis showed the AA homozygous state.

A cine-esophagram demonstrated a greater than 90% upper esophageal stricture at the level of the thoracic inlet (Fig 2A), and the patient was noted to aspirate during the study. Esophagoscopy revealed a smooth, benign-appearing upper esophageal stricture, and an esophageal biopsy showed chronic inflammation. The patient was started on a regimen of iron therapy with plans to dilate her stricture as an outpatient; no other specific dietary manipulations were undertaken. The patient failed follow-up until 1 year later, when she returned with complete resolution of her dysphagia, weight loss, and anemia. A follow-up cine-esophagram at that time showed no aspiration and a less than 30% residual stenosis (Fig 2B). A repeated hematologic evaluation demonstrated a WBC count of 2,900 cells/mm^3, hematocrit of 38.4%, reticulocyte count of

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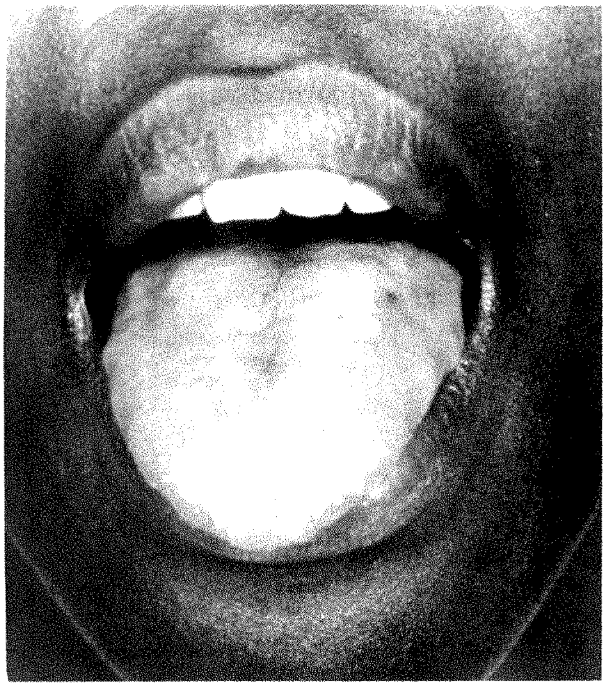

Fig 1. Patient's tongue. Note atrophy of filiform papillae.

1.1 cells/mm^3, platelet count of 410,000 cells/mm^3, MCV of 99 fL, albumin of 4.7 g/dL, TIBC of 390 μg/dL, serum iron of 110 μg/dL, and ferritin of 200 ng/dL.

DISCUSSION

The patient presented in this report provides evidence that iron deficiency plays an important role in the pathogenesis of PVS. First, the patient's iron deficiency clearly preceded the onset of both her dysphagia and her upper esophageal stricture. Second, with iron supplementation alone, she resolved her iron deficiency, dysphagia, and esophageal stricture.

The cause of PVS has been attributed to a number of factors, including hysteria,[3] disturbances in esophageal innervation,[2] autoimmune reactivity,[6,7] infection,[7] nutritional deficiencies,[7] syphilis,[8] and ectopic gastric mucosa.[9] Sporadic reports in the medical literature have noted the resolution of symptoms with iron repletion alone, or in combination with esophageal dilation.[5,10] The role of iron deficiency in the pathogenesis of this disease, and the importance of iron repletion in the treatment of PVS, has yet to be defined and remains a point of debate.

Early authors attributed the anemia in PVS to malnutrition resulting from dysphagia.[1,3] In contrast, Cameron[11] reported that anemia clearly preceded the onset of the dysphagia in 20% of cases. To better understand the relationship between the anemia and the dysphagia, several authors examined the incidence of iron deficiency in patients with esophageal webs and/or stenosis. Two studies have shown an equal incidence of iron deficiency in adult patients with hypopharyngeal webs and in control groups.[12,13] In contrast, a 66% association of iron deficiency anemia with esophageal stricture was demonstrated by Shamma'a,[5] from the Massachusetts General Hospital. Similarly, a Swedish study found that 50% of patients with postcricoid webs or strictures were iron-deficient at the time of presentation, and an additional 38% gave an unequivocal history of iron deficiency anemia.[6] In the past, both iron deficiency anemia and PVS have been endemic in northern Sweden, but today, with improved nutrition and iron supplementation, they are both becoming rare.[14]

The failure to observe either anemia or low ferritin levels in patients with webs does not exclude the possibility that such patients are in fact iron-deficient but not manifesting the anemia.[15,16] Walden-

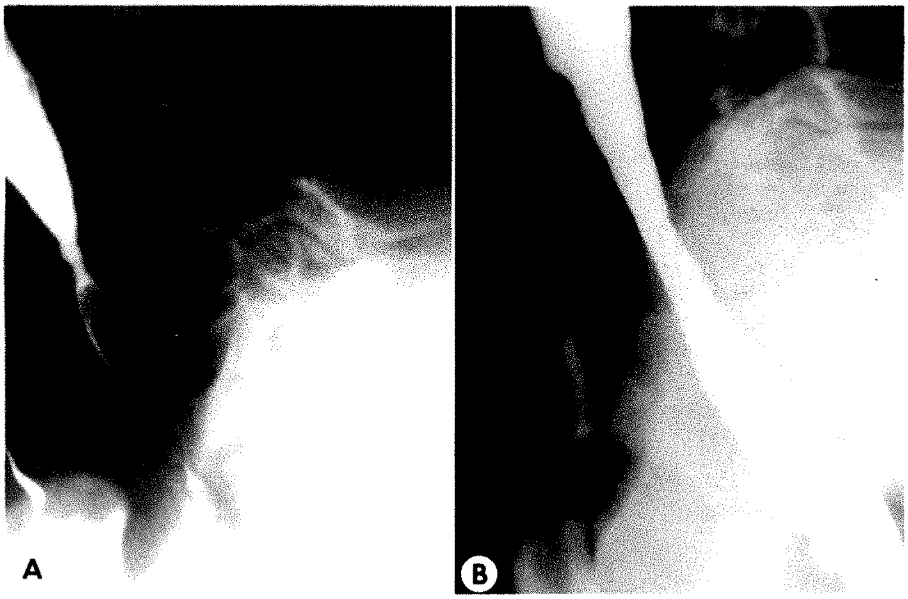

Fig 2. Barium esophagrams. A) At time of presentation, prior to iron repletion. Note high-grade stricture (greater than 90%) in upper esophagus. B) One year after presentation, following iron supplementation. Note resolution of high-grade stricture demonstrated in A.

strom[10] coined the term "sideropenic anemia" for those patients with characteristic epithelial signs and low serum iron but without anemia. It would seem appropriate that all patients with upper esophageal dysphagia and/or stricture be carefully questioned regarding a history of iron deficiency and have screening serum iron tests performed.

Many authors agree that although iron deficiency appears to be a necessary factor for the development of PVS, only a minority of all iron-deficient patients ultimately manifest the syndrome.[6,17,18] Individual patient factors, acting in concert with iron deficiency, may therefore play a role in the development of PVS. Genetic, environmental, and immunologic factors have been examined.[6,18] Patients with PVS have been studied for similarities in human leukocyte antigen groupings; however, no association was found.[17] Chisholm[6] examined the relationship of autoimmunity and PVS by determining the incidence of autoimmune antibodies in iron-deficient patients both with and without webs, and compared this to a normal control group. A significantly higher incidence of autoantibodies was found in both iron-deficient patient groups than in control subjects. No significant difference was found between iron-deficient patients with webs and iron-deficient patients without webs. These findings suggest that iron deficiency is associated with a higher incidence of autoantibodies irrespective of the presence of an esophageal web, but does not support the role of autoimmune reactivity in PVS.

The cause of the dysphagia in PVS has been equally confusing. Some have attributed the swallowing difficulties in PVS patients to a fixed mechanical obstruction,[4,18] whereas others have felt that upper esophageal spasm was the cause of the dysphagia.[2] Dysphagia in PVS has been reported in patients with an anatomically normal esophagus, and recently, the dysphagia in PVS has been attributed to muscular impairment in food propulsion.[19] Administration of iron normalized the decreased swallowing pressures demonstrated by esophageal manometry in these patients. This provides further evidence that iron deficiency has an etiologic role in PVS and may help explain why some PVS patients with dysphagia who have an endoscopically normal esophagus may note resolution of symptoms with iron therapy alone.

For many years, the effect of iron deficiency on iron-dependent enzymes was generally ignored, although abundant clinical evidence suggested that changes in hemoglobin content alone could not explain all of the abnormalities in iron-deficient patients. Impairments of oxidative phosphorylation and DNA replication,[20] as well as decreased levels of cytochrome *c*,[21] have been demonstrated. It is also apparent that the effects of iron deficiency and subsequent repletion are tissue-specific. For example, Dalman[21] demonstrated that when iron-deficient rats are treated with iron, cytochrome *c* concentration returns to normal within 2 days in intestinal mucosa, whereas 40 days was required for muscle to reach normal levels. Organs with a high cell turnover, such as the alimentary tract, rapidly lose activity of iron-dependent enzymes with iron deficiency and are therefore particularly sensitive to the effects of this deficiency.[22]

The alimentary tract is likely to manifest the effects of iron depletion in a number of ways. Glossitis is reported in 39% of iron-deficient patients[23]; this condition usually resolves after several weeks of iron therapy.[24] The buccal and oral mucosa of iron-deficient patients often shows abnormalities including atrophy, increased numbers of mitotic figures, subepithelial inflammation,[22,25] abnormal keratinization, and nuclear abnormalities.[26] Iron deficiency can also cause chronic gastritis, which improves with iron therapy and worsens with recurrent anemia.[27] The gastric mucosa of younger adult patients recovers more quickly following iron therapy than does that of older adult patients.[27] It may be that the favorable response of PVS patients to iron repletion depends on both the patient's age and the chronicity of iron deficiency. This may explain why the young patient presented in this case report responded so well to iron therapy without the need for esophageal dilation.

Despite the documented histologic changes seen in iron-deficient patients, the pathologic importance of these findings to the development of postcricoid carcinoma is poorly understood. There is general agreement that patients with PVS have a higher incidence of postcricoid squamous cell carcinoma.[6,14,28,29] Larsson et al[14] have reported that the incidence of postcricoid carcinoma in Swedish women has declined at the same rate as the incidence of iron deficiency. Furthermore, they found that in the past most patients with postcricoid carcinoma were anemic nonsmoking women, whereas today postcricoid carcinoma is more commonly found in smoking men.[14] Owen[30] has reported a 15% incidence of postcricoid carcinoma in a prospective study of 34 patients with PVS. Similarly, patients with postcricoid carcinoma were 7 times more likely to have a history of chronic dysphagia, and 12 times more likely to have a history of previous esophageal stricture.[28] It is possible that reflux of acidic stomach contents with pooling of secretions above the stricture may contribute to the development of cancer.[31] Alternatively, the histologic changes found in the mucosa of iron-deficient patients could be premalignant. Whatever the cause, the occurrence of postcricoid carcinoma in patients with PVS is too frequent to be entirely adventitious.

This case report demonstrates the importance of iron repletion in the management of PVS. Although the relative importance of other factors such as autoimmunity, duration of iron deficiency, and genetic makeup remains to be elucidated, this case report supports the etiologic role of iron deficiency in the development of PVS. Patients who present with cervical dysphagia with or without stricture may harbor either clinically overt or silent iron deficiency. A careful search should be made for iron deficiency in all patients presenting with either dysphagia or upper esophageal webs/strictures. Iron repletion alone may successfully treat the patient's dysphagia and reverse an upper esophageal stricture without the need for esophageal dilation. The risk of postcricoid carcinoma in these patients warrants careful clinical follow-up.

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HUMAN PAPILLOMAVIRUS IN SQUAMOUS CELL CARCINOMA, LEUKOPLAKIA, LICHEN PLANUS, AND CLINICALLY NORMAL EPITHELIUM OF THE ORAL CAVITY

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Tissue specimens of carcinoma, leukoplakia, and clinically normal epithelium obtained at sites separate from the lesions were examined for the presence of human papillomavirus (HPV). Twenty-two paraffinized specimens of previously diagnosed oral lichen planus were also studied. The carcinoma and leukoplakia specimens were examined by Southern transfer hybridization and reverse blot hybridization; specimens HPV-positive by Southern hybridization were additionally examined by in situ hybridization and an immunoperoxidase technique. The lichen planus specimens were examined by in situ hybridization and immunoperoxidase techniques only. The HPV identification rates were in the range reported in previous studies, and the detection rates were similar for carcinoma, leukoplakia, histologically normal epithelium, and lichen planus. The clinical significance of HPV presence in carcinoma, leukoplakia, and lichen planus was not evaluable because of the short duration of follow-up.

KEY WORDS — carcinoma, epithelium, human papillomavirus, koilocytosis, leukoplakia, lichen planus.

INTRODUCTION

Detection of human papillomavirus (HPV) in selected epithelial lesions of the oral cavity is the subject of this report. Specimens included in the study are squamous cell carcinoma, leukoplakia, lichen planus, and clinically normal epithelium obtained at sites separate from disease sites. This study was undertaken to extend prior observations regarding the prevalence of HPV in benign, premalignant, and malignant epithelial disorders of oral mucosa.

On the basis of clinical observation, upper aerodigestive tract (UADT) squamous cell carcinoma is preceded by clinical leukoplakia in an undefined subset of cases. "Leukoplakia" is a clinical term describing a white patch that encompasses a wide spectrum of histopathologic disorders ranging from hyperkeratosis, dysplasia, and carcinoma in situ to squamous cell carcinoma. Lichen planus is an oral mucosal disorder that is infrequently a cancer precursor.[1]

Fifty-eight distinct HPV types have been identified to date. An epitheliotropic DNA virus, HPV predominantly infects skin and mucosal lining in the genital and UADT regions. Of the 58 HPV types, 34 are predominantly associated with skin lesions, and 22 with genital mucosal lesions. The oral cavity is infected with a variety of HPVs.[2] Both HPV-13[3] and HPV-32[4] are primarily infections of the oral cavity and are associated with focal epithelial hyperplasia. Both HPV-30 and HPV-57 have also been recovered from the oral cavity (de Villiers; unpublished observations). In addition, genital tract HPV types 6, 11, and 16 and cutaneous HPV type 2 have been identified in benign and malignant lesions of the oral cavity.[5-9] Recurrent respiratory papillomatosis is associated with HPV-6 and HPV-11.[2] Squamous cell carcinomas of the male and female genital tracts have a well-established association with HPV-16 and HPV-18.[10]

Human papillomavirus cannot be grown in culture; however, recent developments in laboratory techniques have enabled investigators to document HPV by immunoperoxidase detection of capsid antigen,[11] identification of type-specific HPV DNA by Southern hybridization,[12] in situ hybridization,[13] and reverse blot hybridization.[14] A new and potent technique of polymerase chain reaction has recently become available for virus identification.[15]

In this study, the prevalence of HPV in specified oral lesions was investigated to determine whether the presence of HPV identifies lesions at increased risk of developing into squamous cell carcinoma.

MATERIALS AND METHODS

Patient Accrual. Tissue specimens of oral squamous cell carcinoma and leukoplakia were accrued from patients receiving treatment in the Department of Otolaryngology–Head and Neck Surgery at The Johns Hopkins Hospital and at the Dental School, University of Maryland, Baltimore. We were unable to identify and accrue tissue from patients with lichen planus; therefore, paraffin blocks

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TABLE 1. HUMAN PAPILLOMAVIRUS IDENTIFICATION ACCORDING TO EXAMINATION TECHNIQUE

Technique	*No. Tested*	*No. HPV-Positive*	*Type*
Southern transfer hybridization	119	6 (5%)	2 HPV-6 2*HPV-11 2 HPV-16 0 HPV-18 0 HPV-31
Reverse blot hybridization	105	3 (3%)	1 HPV-3-related 1 HPV-13-related 1 HPV-57-related
Immunoperoxidase	31	4 (13%)	None specified
In situ hybridization	31	0	0

HPV — human papillomavirus.

*Leukoplakia.

of 22 specimens of previously diagnosed lichen planus were obtained from The Johns Hopkins Hospital Oral Pathology biopsy service.

Informed Consent. Informed consent was obtained prior to specimen collection. The purpose of the present study was explained to each patient in whom biopsy or excision of an oral lesion was proposed. The biopsies were relevant to the diagnosis and appropriate for management of each patient.

Specimen Accrual. Tissue specimens were obtained at biopsy or at surgical resection. Biopsy specimens of small lesions, usually leukoplakia, were removed with the patient under local anesthesia in the outpatient dispensary. Carcinoma specimens were obtained at surgical resection so that patient discomfort and apprehension could be minimized and an adequate specimen size could be assured. Whenever possible, three biopsy specimens were obtained from each patient: one from the central portion of the lesion (called herein specimen A), one from the periphery of the lesion (specimen B), and one from clinically normal tissue at a corresponding contralateral site (specimen C). Each biopsy specimen was immediately divided in two; one portion was submitted for routine hematoxylin and eosin staining for light microscopic examination, and a second portion was snap-frozen in liquid nitrogen and preserved for HPV detection.

A total of 141 specimens obtained from 80 patients were accrued for this study. Seventy-four fresh specimens were obtained from 29 patients with cancer, 45 fresh specimens were obtained from 30 patients with leukoplakia, and 22 paraffinized specimens were obtained from 21 patients with lichen planus. Fresh specimens were examined by Southern hybridization and reverse blot hybridization techniques, and paraffinized specimens were examined by in situ hybridization and immunoperoxidase techniques.

Histopathology. Histologic slides were reviewed to confirm the diagnoses and to note whether "viral changes" (eg, koilocytosis) were present.

VIRAL DIAGNOSTIC EXAMINATION

Southern Hybridization. Biopsy specimens were snap-frozen in liquid nitrogen and stored at −70°C until processed and hybridized as described.[5] Extracted DNA (about 15 μg when available) was digested with restriction endonuclease PstI and transferred to nylon filters with a Vacu-Blot apparatus. Filters were hybridized first with a mixed probe (HPV-6, -11, -16, -18, and -31) and sequentially with individual probes after the previous probe had been washed off. The hybridized filters were autoradiographed for up to 7 days. Positive control filters were included to monitor the sensitivity of the tests, which was estimated to be one genome copy per cell. The presence of virus was determined by hybridization patterns at melting temperature, −17°C.

In Situ Hybridization. Paraffin sections of tissues positive by Southern hybridization were placed on organosilane-treated slides and examined for the presence of HPV transcripts by in situ hybridization with single-stranded ^{35}S-labeled antisense RNA probes of HPV-6, -11, -16, -18, and -31.[13] Sections known to contain viral sequences that hybridized with the probes were included as positive controls.

Immunoperoxidase. Paraffin sections of virus-positive carcinoma and leukoplakia specimens and of lichen planus were stained as described[11] for viral capsid antigen by the immunoperoxidase test using genus-specific rabbit antiserum. Sections known to contain HPV antigen served as controls.

Reverse Blot Hybridization. These tests were performed at the German Cancer Research Center, Heidelberg, Federal Republic of Germany, on all specimens from which adequate amounts of DNA

TABLE 2. HUMAN PAPILLOMAVIRUS IN ORAL CARCINOMA IN 74 SPECIMENS FROM 29 PATIENTS

Primary Cancer Site	*No. Pts*	*Male/Female*	*No. Specimens*	*Koilocytosis*	*HPV-Positive*	*Specimen Site*	*Technique*
Floor of mouth	7	4/3	22	6	2 HPV-16	B,C	SH
Tongue	9	5/4	20	9	1 HPV-57-related 1 HPV-3-related	A A	RB RB
Alveolar mucosa	3	2/1	8	3	1 HPV-6	C	SH
Palate	5	4/1	11	4	1 HPV-6	A	SH
Tonsil	2	1/1	5	2	1 HPV-13-related	A	RB
Retromolar trigone	3	3/0	8	3	0		
Total	29	19/10	74	26	7		

A — central portion of tumor, B — peripheral portion of tumor, C — normal epithelium, SH — Southern hybridization, RB — reverse blot.

TABLE 3. HUMAN PAPILLOMAVIRUS IN ORAL LEUKOPLAKIA IN 45 SPECIMENS FROM 30 PATIENTS

Lesion Site	*No. Pts*	*Male/ Female*	*No. Specimens*	*Koilocytosis*	*HPV-Positive*	*Specimen Site*	*Technique*
Lip	1	1/0	1	1	0		
Floor of mouth	3	2/1	6	2	0		
Tongue	7	6/1	12	4	2 HPV-11	A,C	SH
Buccal mucosa	8	7/1	9	2	0		
Palate	3	2/1	6	1	0		
Alveolar mucosa	7	4/3	10	4	0		
Retromolar trigone	1	1/0	1	4	0		
Total	30	23/7	45	18			

For definition of A, C, and SH, see Table 2.

were available. Briefly, 0.5 to 1.0 μg of cellular DNA was labelled by nick translation with ^{32}P and hybridized with genomic DNAs of HPV-1 to HPV-57 blotted onto nylon filters. The technique is estimated to be sensitive enough to detect 10 copies of genome per cell.[14]

RESULTS

Human Papillomavirus Detection. Human papillomavirus DNA was identified in 6 of 119 tissue samples (5%) tested by Southern hybridization (Table 1). In all instances, the viral genome was present in low copy numbers and in an unintegrated state. Three additional specimens were positive for the virus by reverse blot assays. Thus, a total of 9 of 119 specimens (8%) had evidence of HPV DNA.

Carcinoma. Seven of 74 specimens from patients with carcinoma had HPV DNA; detections in 4 specimens from three patients were made by Southern hybridization, and in 3 specimens from three additional patients, by reverse blot hydridization (Table 2). Four HPV-positive specimens were from the central portion of tumor, 1 was obtained from the tumor periphery, and 2 were from clinically and histologically normal epithelium.

Specimens that were HPV-positive by Southern hybridization were obtained from three patients: HPV-positive specimens B and C were obtained from a 67-year-old man with T2N1M0 carcinoma of the floor of the mouth, an HPV-positive specimen B was obtained from a 68-year-old man with T1N0M0 carcinoma of the palate, and a specimen C was obtained from a 56-year-old woman with T2N1M0 carcinoma of the alveolar mucosa. The specimens that were HPV-positive by reverse blot hybridizations were all observed in central tumor tissue (A): one was from a 50-year-old woman with T2N1M0 carcinoma of the tongue, one was from a 67-year-old woman with T2N0M0 carcinoma of the tongue, and one was from a 73-year-old man with T3N1M0 carcinoma of the tonsil.

Leukoplakia. Two leukoplakia specimens testing HPV-positive were specimens A and C from a 27-year-old man with a history of juvenile-onset recurrent respiratory papillomatosis (Table 3). This base of tongue lesion was a shaggy flat leukoplakia histologically diagnosed as papilloma (A); specimen C was clinically and histologically normal.

Lichen Planus. Four of 22 lichen planus specimens tested positive for HPV capsid antigen; all were from women (Table 4). Two were from buccal mucosa, one was from alveolar mucosa, and one was from the tongue. None of the 22 specimens was positive by in situ hybridization with HPV-6, -11, -16, -18, and -31 probes.

HISTOPATHOLOGY

Carcinoma. Twenty-eight of 29 patients with cancer were confirmed to have squamous cell carcinoma; one had adenocarcinoma. Koilocytes, defined as large epithelial cells with vacuolated cytoplasm and an eccentric pyknotic nucleus, were identified in 26 of 28 squamous cell carcinoma specimens; the (single) adenocarcinoma specimen also showed koilocytosis. Of the 2 of the 29 patients who were nonsmokers, one specimen was HPV-positive and demonstrated koilocytosis.

Leukoplakia. Among leukoplakia specimens, 2 showed carcinoma in situ, 2 dysplasia, and 3 papilloma (Table 5). The remainder had hyperorthokeratosis and/or hyperparakeratosis. Hyperorthokeratosis is defined as anuclear thickening of the stratum corneum; hyperparakeratosis is defined as thicken-

TABLE 4. HUMAN PAPILLOMAVIRUS IN ORAL LICHEN PLANUS IN 22 SPECIMENS FROM 21 PATIENTS

Lesion Site	*No. Pts Male/Female*	*No. Specimens*	*Koilocytosis*	*Erosive Lichen Planus*	*HPV-Positive*	
					ISH	*PAP*
Lip	1/0	1	0	1	0	0
Buccal mucosa	3/12	15	5	6	0	2
Alveolar mucosa	0/4	4	2	0	0	1
Tongue	0/1	1	0	1	0	1
Retromolar trigone	1/0	1	1		0	
Total	5/17	22	8	8	0	4

ISH — in situ hybridization, PAP — peroxidase-antiperoxidase.

TABLE 5. HUMAN PAPILLOMAVIRUS IN ORAL LEUKOPLAKIA ACCORDING TO HISTOLOGIC TYPE

Diagnosis	*No. Pts*	*Koilocytosis*	*HPV-Positive*
HO	6	4	0
HP	9	4	0
HO or HP	7	2	0
Dysplasia	2	1	0
Carcinoma in situ	2	1	0
Papilloma	3	3	1 HPV-11
Total	29	15	

HO — hyperorthokeratosis, HP — hyperparakeratosis.

ing of the stratum corneum by nucleated epithelial cells. Fifteen of 29 leukoplakic specimens exhibited koilocytosis.

Lichen Planus. Lichen planus was defined by the standard criteria: squamatization of the basal cell layer and its replacement by an eosinophilic band, and a dense lymphocytic or lymphohistocytic infiltrate immediately subjacent to the epithelium. Koilocytes were present in 8 of 22 specimens.

DISCUSSION

The objectives of this study were to determine 1) whether HPV could be detected in oral carcinoma and its putative precursors — namely, leukoplakia and lichen planus, 2) whether histologic features (specifically koilocytosis) are predictive of HPV presence, and 3) whether specific HPV types could prognosticate clinical course.

Human papillomavirus was present in seven specimens from six carcinoma patients; koilocytes were present in all HPV-positive specimens and were present in 21 of 23 HPV-negative specimens as well. Human papillomavirus was detected in two normal tissue samples obtained from a contralateral corresponding site to the carcinoma; in one of these, the cancer specimen was HPV-negative. The HPV types identified were HPV-6 and HPV-16 by Southern blot hybridization and HPV-3-related, HPV-13-related, and HPV-57-related by reverse blot hybridization. Only 2 of 29 cancer patients were nonsmokers, but HPV was detected in a 50-year-old nonsmoking woman with tongue cancer who had no other obvious risk factors for oral cancer. One HPV-positive patient with palatal cancer had a history of a prior metachronous retromolar trigone

TABLE 6. HUMAN PAPILLOMAVIRUS IN ORAL CANCERS: SUMMARY OF FINDINGS IN 29 PATIENTS

Pt No.	*Age*	*Sex*	*No. of Specimens*	*Site*	*Histologic Diagnosis*	*Koilocytes*	*Southern or Reverse Blot Hybridization* A	B	C	*Carcinoma In Situ*	*Papilloma*	*Comments*
1	62	F	3	FOM	SCC	+						
2	65	M	4	FOM	SCC	+						
3	67	M	3	FOM	SCC	+		16	16	Negative	Negative	
4	54	M	3	FOM	SCC	+						
5	67	M	3	FOM	SCC	+						
6	52	F	4	FOM	SCC	–						
7	71	F	2	FOM	SCC	+						
8	63	M	2	Tongue	SCC	+						
9	50	F	2	Tongue	SCC	+	3					Nonsmoker
10	78	M	3	Tongue	Adenoca	+						
11	60	F	2	Tongue	SCC	+						Nonsmoker
12	79	M	1	Tongue	SCC	+						
13	69	M	2	Tongue	SCC	+						
14	67	M	1	Tongue	SCC	+						
15	67	F	1	Tongue	SCC	+	57					
16	79	F	1	Tongue	SCC	+						
17	56	F	3	Alv muc	SCC	+						
18	59	M	4	Alv muc	SCC	+			6	Negative	Negative	Heavy metal isotope exposure
19	67	M	1	Alv muc	SCC	+						
20	68	M	2	Palate	SCC	+	6			Negative	Negative	History of RMT cancer
21	63	M	1	Palate	SCC							History of skin cancers
22	52	M	3	Palate	SCC	+						
23	77	F	1	Palate	SCC	+						
24	51	M	1	Palate	SCC	+						
25	73	M	2	Tonsil	SCC	+	13*					
26	66	F	1	Tonsil	SCC	+						
27	56	M	2	RMT	SCC	+						
28	49	M	1	RMT	SCC	+						
29	64	M	1	RMT	SCC	+						

For definition of specimens A, B, and C, see Table 2.

FOM — floor of mouth, Alv muc — alveolar mucosa, RMT — retromolar trigone, SCC — squamous cell carcinoma, Adenoca — adenocarcinoma, blank spaces — not tested.

*Reverse blot.

TABLE 7. HUMAN PAPILLOMAVIRUS IN ORAL LEUKOPLAKIA: SUMMARY OF FINDINGS IN 30 PATIENTS

Pt No.	*Age*	*Sex*	*No. of Specimens*	*Site*	*Histologic Diagnosis*	*Koilocytes*	*Southern or Reverse Blot Hybridization*			*Carcinoma In Situ*	*Papilloma*	*Comments*
							A	*B*	*C*			
30	54	M	1	Lip	CIS	+						
31	34	M	1	FOM	HP	+						
32	43	M	1	FOM	HP	+						
33	47	F	1	FOM	HP	–						
34	61	M	3	Tongue	CIS	–						
35	37	M	3	Tongue	HO,HP	+						
36	55	M	1	Tongue	HP	+						Nonsmoker
37	27	M	2	Tongue	Pap	+	11		11	Negative	Negative	History of RRP
38	18	F	1	Tongue		–						Nonsmoker
39	50	M	1	Tongue	HP	–						Nonsmoker
40	36	M	1	Tongue	HP	+						
41	46	M	1	Buc muc	HP	–						
42	67	M	1	Buc muc	HO	+						
43	58	M	1	Buc muc	HO	+						
44	32	M	1	Buc muc	HO,HP	–						
45	34	M	1	Buc muc	HP	–						
46	56	M	1	Buc muc	HO	–						Nonsmoker
47	62	M	1	Buc muc	HP	–						Chewing tobacco
48	66	F	1	Buc muc	HO,HP	–						
49	45	F	1	Palate	Pap	+						
50	52	M	1	Palate	HO	–						
51	64	M	1	Soft pal	Mod dysp	–						
52	51	M	4	Alv muc	Pap	+						Plantar wart
53	60	M	1	Alv muc	HO	+						
54	72	M	1	Alv muc	HO	+						
55	71	F	1	Alv muc	HO,HP	–						Nonsmoker
56	48	M	1	Alv muc	HO,HP	–						
57	73	F	1	Alv muc	HO,HP	–						
58	64	F	1	Alv muc	HO,HP	+						Nonsmoker
59	57	M	1	RMT	Severe dysplasia	+						

For definition of specimens A, B, and C, see Table 2.

FOM — floor of mouth, Buc muc — buccal mucosa, Soft pal — soft palate, Alv muc — alveolar mucosa, RMT — retromolar trigone, CIS — carcinoma in situ, HP — hyperparakeratosis, HO — hyperorthokeratosis, Pap — papilloma, Mod dysp — moderate dysplasia, RRP — recurrent respiratory papillomatosis, blank spaces — not tested.

carcinoma. This identification of HPV was notable in two respects: first, the documentation of viral presence in apparently normal epithelium, and second, the possible relevance of HPV to the occurrence of two separate carcinomas arising at separate times (Table 6).

The two HPV-positive leukoplakia specimens were obtained from a patient with a history of juvenile-onset recurrent respiratory papillomatosis. The first specimen (A) from the base of the tongue was a flat, shaggy leukoplakic patch, not at all typical of papilloma; the second specimen (B), obtained from clinically and histologically normal base of tongue mucosa contralateral to the leukoplakic lesion, was positive for HPV. Koilocytosis was present in the HPV-positive specimens and in 15 of 30 leukoplakia patients. Two other subjects had clinical leukoplakia–histologic papilloma: one of the palate and one of alveolar mucosa; both lesions were HPV-negative. Of the 29 leukoplakia specimens, 22 displayed hyperkeratosis, 2 showed carcinoma in situ, and 2 showed dysplasia; HPV was not detected in any of the above (Table 7). This contrasts with an earlier study of laryngeal leukoplakia in which 20 of 60 specimens (obtained from 14 of 20 patients) were HPV-positive.[16]

Four of 22 lichen planus specimens were HPV-positive by immunoperoxidase examination and HPV-negative by in situ hybridization. The HPV type in these lesions has not yet been established. The HPV-positive lichen planus specimens were obtained from buccal mucosa in two cases, from the maxillary alveolus in one case, and from the tongue in one case. All four HPV-positive subjects were women, and two of four showed koilocytes (Table 8). Maitland et al[9] reported HPV DNA in seven of eight lichen planus specimens.

Southern blot hybridization is regarded as the most sensitive and specific examination for detecting HPV infection. Six of the nine HPV identifications were achieved by Southern blot hybridization using probes for HPV-6, -11, -16, -18, and -31. The three additional HPV identifications were made by screening the tissue DNAs in a reverse blot hybridization.

TABLE 8. HUMAN PAPILLOMAVIRUS IN ORAL LICHEN PLANUS: SUMMARY OF FINDINGS IN 22 BIOPSY SPECIMENS FROM 21 PATIENTS

Pt No.	*Age*	*Sex*	*Site*	*Clinical Erosive Lichen Planus*	*Koilocytosis*	*In Situ Hybridization*				*Papilloma*
						6/11	*16*	*18*	*31*	
60	77	M	Lower lip	+	–	–	–	–	–	–
61	46	M	Buccal mucosa	+	–	–	–	–	–	–
62	76	F	Buccal mucosa	+	–	–	–	–	–	–
63	59	F	Buccal mucosa	–	+	–	–	–	–	–
	59	F	Buccal mucosa	–	–	–	–	–	–	–
64	48	F	Buccal mucosa	–	–	–	–	–	–	–
65	47	F	Buccal mucosa			–	–	–	–	–
66	53	F	Buccal mucosa	NS	–	–	–	–	–	–
67	62	F	Buccal mucosa	+	–	–	–	–	–	–
68	67	F	Buccal mucosa	+	–	–	–	–	–	–
69	23	F	Buccal mucosa	+	–	–	–	–	–	–
70	32	F	Buccal mucosa	NS	+	–	–	–	–	–
71	40	M	Buccal mucosa	–	+	–	–	–	–	–
72	63	M	Buccal mucosa	+	+	–	–	–	–	–
73	49	F	Buccal mucosa	–		–	–	–	–	+
74	61	F	Buccal mucosa	NS	+	–	–	–	–	+
75	37	F	Buccal vestibule	NS	–	–	–	–	–	–
76	69	F	Mandibular vestibule	NS	+	–	–	–	–	–
77	66	F	Mandibular alveolus	NS	–	–	–	–	–	–
78	62	F	Maxillary alveolus	–	+	–	–	–	–	+
79	70	F	Lateral border of tongue	+	–	–	–	–	–	+
80	72	M	Pad of retromolar trigone	–	+	–	–	–	–	–

NS — not specified.

Reverse blot hybridization was performed to detect HPV other than HPV-6, -11, -16, -18, and -31, and detected positive signals to HPV-3, -13, and -57. Upon subsequent hybridization by Southern blot technique, DNA sequences related but not identical to complete DNA genomes of these three viruses, respectively, could be identified. Because of the lack of sufficient DNA samples, it could not be determined whether these biopsy specimens contained integrated partial HPV genomes or related, but not yet characterized, new HPV types. Human papillomavirus 13 has been associated with focal epithelial hyperplasia, a benign oral lesion not considered to be precancerous; HPV-3 is commonly detected in cutaneous warts, and its presence in oral lesions can be regarded as probable skin-to-mouth transfer. Human papillomavirus 57 has been isolated from an inverted papilloma of the maxillary sinus. Reverse blot hybridization can test for any and all characterized HPV types and, thus, is well suited as a comprehensive screening examination. Specimens positive by reverse blot hybridization are reexamined by Southern blot for confirmation.

The immunoperoxidase examination utilizes a rabbit antibody that reacts with genus-specific HPV antigen. This examination is useful in screening for HPV, but is the least sensitive of the four techniques used in this study and does not specify HPV type.

In situ hybridization detects HPV DNA in the cell nucleus, thereby identifying the virus-infected cell. Either a specific HPV type or a mixed probe can be used in this test. Radioactive probes (^{35}S, ^{32}P, and ^{3}H) and nonisotopic probes are regarded as having similar detection thresholds. Specimens negative by in situ hybridization but positive by the immunoperoxidase test may represent HPVs not yet characterized and identified (typed).

Koilocytosis was noted in 26 of 29 carcinoma patients, in 15 of 30 leukoplakia patients, and in 7 of 22 lichen planus specimens. All HPV-positive carcinoma and leukoplakia specimens were from patients with koilocytosis, and 2 of 4 HPV-positive lichen planus specimens exhibited this cell type. Neither koilocytosis nor HPV positivity was segregated on the basis of sex or anatomic site. The significance of so-called viral changes (koilocytosis) is not known. While all HPV-positive specimens of leukoplakia and squamous cell carcinoma demonstrated koilocytosis, virus was not demonstrated in the many remaining patients with koilocytosis; these may be patients with low copy numbers or who have HPV types not yet identified. Epithelial cells resembling koilocytes are often found in normal oral mucous membrane, particularly in the buccal mucosa.

The low prevalence rate of HPV in oral lesions in this study is in accord with previously published findings[2] and attests to the irregular distribution and low copy numbers of HPV. Gissmann recently found that 5 of 20 subjects with no clinically apparent infections showed HPV-16 on a single cervical swab. Repeated examinations (up to 10 or 12 swabs) led to HPV identification by polymerase chain reaction (PCR) in 13 of 15 subjects (L. Gissmann, personal communication, 1989). In the current study, HPV identification tended to occur in patients from whom the largest number of specimens was examined. The recently developed PCR technique amplifies the DNA genome, and future studies using this technique are expected to yield higher rates of HPV detection.[1] In a recent report Kiyabu et al,[15] using PCR, identified HPV-16 DNA in 36% of oral cancers; this rate is higher than that found in studies using earlier techniques.

CONCLUSIONS

1. The presence of HPV was demonstrated in squamous cell carcinoma, leukoplakia of various histologic types, and lichen planus occurring in the oral cavity.
2. Human papillomavirus was present in 7 of 74 specimens from 26 of 29 patients with oral cavity squamous cell carcinoma.
3. It was present in 1 of 45 specimens from 1 of 30 patients with leukoplakia.
4. It was present in 3 of 33 specimens of clinically normal epithelium contralateral to squamous cell carcinoma or leukoplakia.
5. It was present in 4 of 22 specimens from 4 of 22 patients with lichen planus.
6. Human papillomaviruses 3, 6, 13, 16, and 57 were identified in squamous cell carcinoma; HPV-11 was identified in leukoplakia; the HPV types in lichen planus were not identified.
7. Koilocytosis was present in 90% of carcinoma specimens, 50% of leukoplakia specimens, and 30% of lichen planus specimens.
8. All HPV detections in oral squamous carcinoma and leukoplakia occurred in the presence of koilocytosis. Two of four HPV detections in lichen planus occurred when koilocytosis was present.
9. The presence of HPV in oral lesions was not evaluable in terms of prognosis.

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QUANTITATIVE STUDY OF THE EARLY EFFECTS OF TRACHEOTOMY AND ENDOTRACHEAL INTUBATION ON THE RABBIT TRACHEOBRONCHIAL TREE

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Histopathologic evaluation of the tracheobronchial tree was performed in 12 rabbits to study the effects of 1 hour of tracheotomy or endotracheal intubation. In five animals who underwent oral endotracheal intubation, epithelial erosions and submucosal inflammation in the proximal (bronchial) airway covered 34.9% and 71.3% of the luminal circumference, respectively. This was highly significant ($p<.001$) against two control animals, in which 4.8% erosion and 3.9% inflammation were observed. Tracheotomy in three animals caused 22.8% bronchial epithelial erosion and 46.0% inflammation, which were not significantly greater than values of 15.0% and 20.6% observed following "sham" tracheotomy. The severity of the proximal (indirect) consequences of endotracheal intubation may have been attributable to the lack of humidification, but this does not explain the lesser damage caused by tracheotomy. It is postulated that increased inspiratory flow rate and pressures occurring in endotracheally intubated animals may be contributory factors.

KEY WORDS — endotracheal intubation, tracheal injury, tracheotomy.

INTRODUCTION

The direct injury caused by intubating the trachea has been extensively studied (reviewed recently by Weymuller[1]), but considerably less attention has been paid to the additional indirect effects upon the proximal tracheobronchial tree. Other factors have been identified that have the potential to damage the respiratory epithelium and impair mucociliary function once the protection of the nasopharynx has been bypassed. These include variations in humidity[2] and temperature[3] of the inspired air and the introduction of mucosal irritants such as cigarette smoke, sulfur dioxide, ammonia, and even some anesthetic agents.[4] Identification of the extent of indirect injury caused by these insults is of considerable importance, as an intact mucociliary mechanism in the lower respiratory tract serves to protect against pulmonary infection.

Previous studies in fetal lambs and beagle puppies suggest that histologic changes occur in the proximal trachea as soon as 3 hours after endotracheal intubation or tracheotomy.[5,6] The purpose of the present study is to observe the consequences of just 1 hour of breathing room air after endotracheal intubation or tracheotomy upon the mucosa and submucosa of the tracheobronchial tree. This early response is of particular relevance to emergency airway management. In addition, a new method of quantitation of these histopathologic changes is described that gives a precise comparison of the extent of the proximal (indirect) damage caused by tracheotomy or endotracheal intubation.

METHODS

Animal Model. Twelve 1.5- to 2.5-kg female New Zealand white rabbits were divided into four experimental groups. Five animals underwent endotracheal intubation, three had a tracheotomy, two had a "sham" tracheotomy, and two served as controls (Fig 1A). The small diameter of the rabbit trachea approximates the premature neonate's trachea,[7,8] and the relatively long trachea provides more than adequate length between the tube tip and carina.

Experimental Techniques. General anesthesia was induced and maintained in all animals with intravenous xylazine (Rompun; 3 mg/kg) followed after a few minutes by intravenous ketamine hydrochloride (10 mg/kg).

The endotracheal tube group was intubated orally with a 2.5-gauge sterile Silastic noncuffed endotracheal tube, precut to reach the midtrachea. All intubations were considered to be uncomplicated.

Tracheotomy was performed by a standard aseptic technique. The shaved neck was incised vertically in the midline, and hemostasis was achieved with chromic catgut ligatures. A vertical-slit tracheotomy was made at the level of the third tracheal ring, without excision of cartilage. A noncuffed Silastic Shiley pediatric 00 tracheotomy tube was inserted and fixed with sutures to the adjacent skin.

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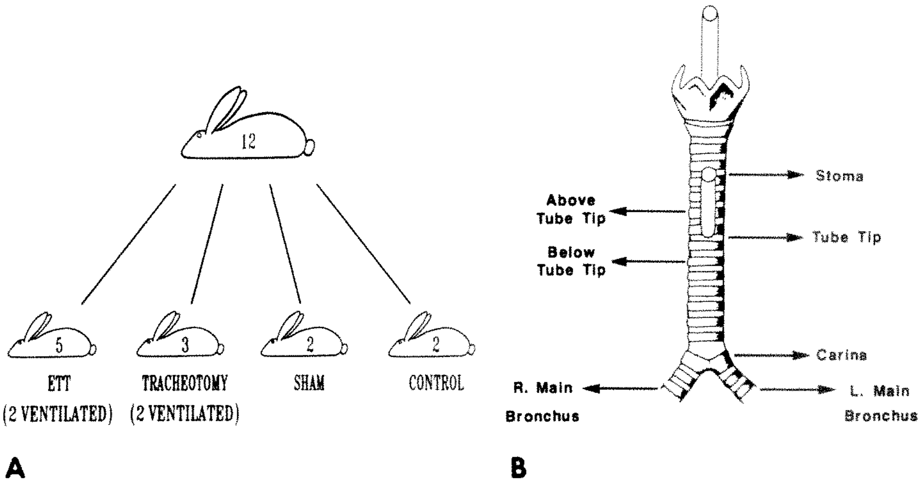
Fig 1. Diagrams of experimental setup. A) Experimental groups. Sham — "sham" tracheotomy. B) Levels of tracheobronchial tree from which sections were taken for histologic examination. "Stoma" sections were cut in tracheotomy and "sham" tracheotomy groups only. For control and "sham" tracheotomy specimens (where there was no tube), single random midtrachea section was cut from region tube would have reached.



"Sham" tracheotomy involved the same procedure as tracheotomy, with the exception that no tube was inserted, and the skin edges were closed with sutures. "Sham" animals breathed normally through their upper airway.

Control rabbits were maintained under anesthesia with no other intervention.

While asleep, four animals (two intubated and two with a tracheotomy) were electively supported by ventilation with nonhumidified air at a rate of 60 breaths per minute and inspiratory pressure of 8 cm H_2O.

Histopathologic Assessment. All animals were killed painlessly at 1 hour by intraperitoneal sodium pentobarbital overdose, and an immediate autopsy was performed. After inspection to confirm tube position, the tracheobronchial tree and lungs were removed en bloc, and segments were taken from up to seven levels (Fig 1B). Specimens were fixed in 10% buffered formalin and placed in paraffin block, and transverse serial sections were stained with hematoxylin and eosin. Two tracheal blocks and one bronchial block, taken from an intubated nonventilated animal, were lost during processing and thus were not analyzed, but there were no deliberate exclusions. A representative section from each block was photographed in black and white, and enlargements were made (approximately 60x magnification). Microscopic evaluation of all sections photographed was carried out by two blinded investigators (S.Y.S. and R.S.), and abnormalities observed microscopically were marked accurately on the corresponding photograph for later measurement (Fig 2).

The following pathologic abnormalities were recorded:

1. Minor epithelial damage: loss of cilia, incomplete loss of columnar cells.
2. Major epithelial damage: complete columnar

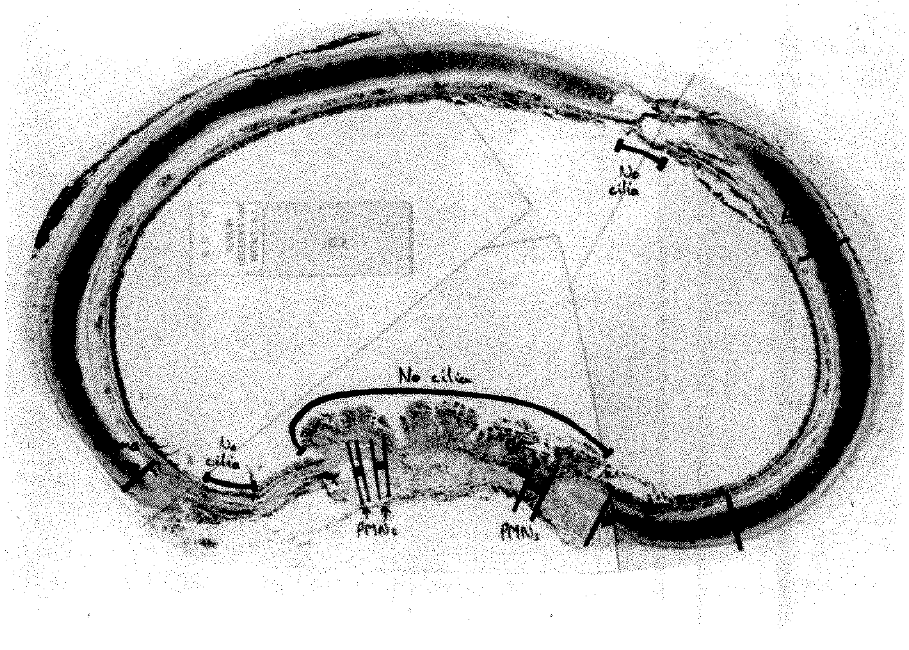


Fig 2. Photographic enlargement on which histologic abnormalities were recorded as they were identified microscopically. Original histologic section is shown for comparison. PMNs — polymorphonuclear leukocytes.

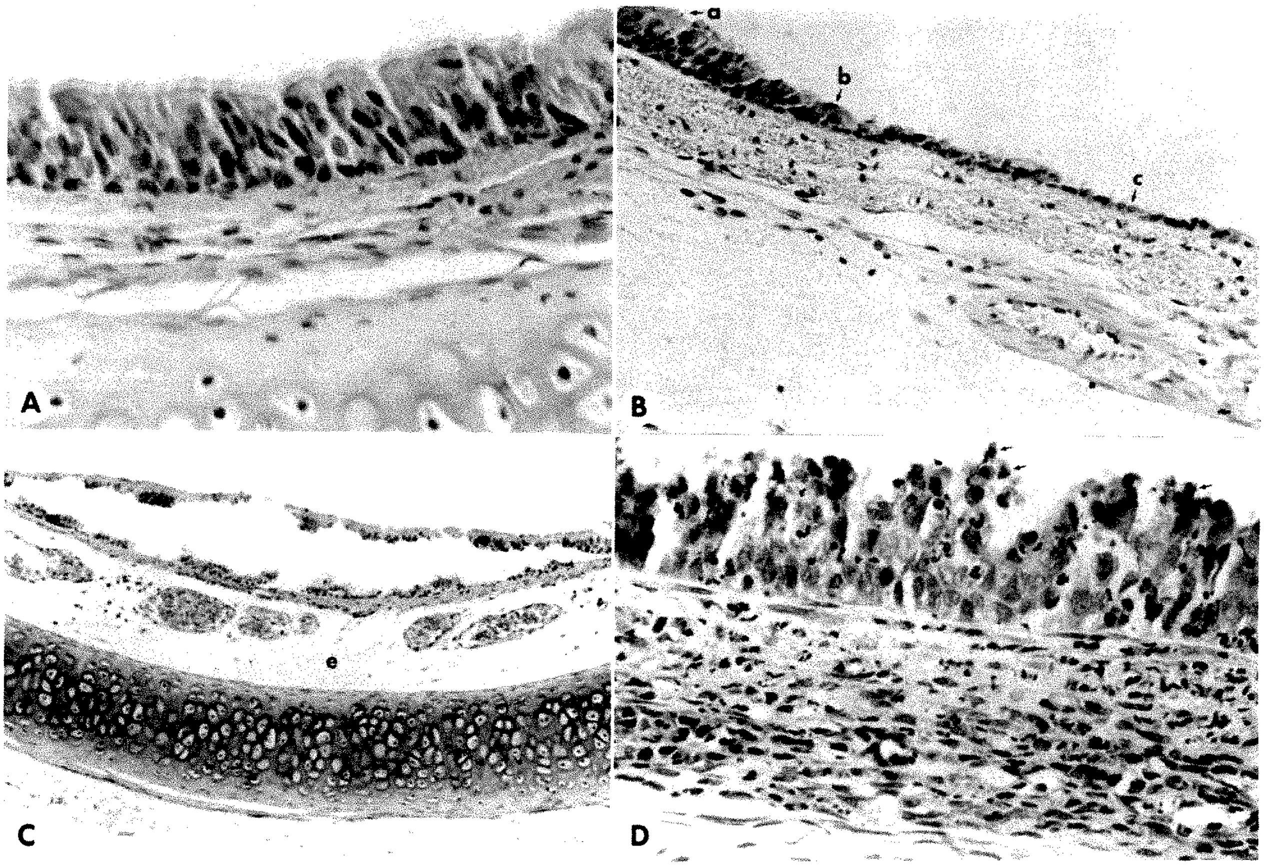


Fig 3. Photomicrographs of rabbit respiratory epithelium. A) Normal epithelium from bronchus of control animal (original x400). B) Tracheal epithelium from intubated rabbit, ranging from normal (a) to "minor" loss (b) to "major" loss (c) (original x250). See text for definitions. C) Trachea of intubated rabbit showing fractured mucosa that was recorded as artifact (original x100). There is obvious submucosal edema (e). D) Bronchus of intubated rabbit showing neutrophils (arrows) penetrating epithelium and about to spill into lumen at site featuring submucosal inflammatory cell infiltration (original x400).

cell loss, absent basal epithelium, loss of basement membrane.

3. Acute inflammation: submucosal edema, polymorphonuclear cells, infiltration.
4. Submucosal hemorrhage.

Discrimination among regions of normal mucosa, minor epithelial loss, and major loss was clear (Fig 3A,B). Loss of epithelium with the appearance of fracture of the mucosa, distinguished by abrupt change with no adjacent abnormality, was considered to be artifactual, secondary to processing the tissue. In some instances the lifted mucosa could be found elsewhere in the same section (Fig 3C). This artifact frequently occurred at sites of submucosal edema and may possibly have represented abnormal friability in the tissue that was then exposed to the trauma of sectioning. Treating fractured epithelium as normal may have resulted in the histopathologic abnormalities' being underscored, an error on the side of caution.

Some sections from both control and experimental animals showed lymphoid follicles and aggregates of chronic inflammatory cells. We believe this to be a normal finding in the respiratory tract of the rabbit, and it was not considered to have any relation to the experimental procedures.

The linear extent of each histopathologic change was measured on every photograph and expressed as a percentage of the total tracheal circumference at that level. For statistical analysis, data from sections of trachea taken at, above, or below the tube tip were grouped together and compared with values from the more proximal sections cut from the carina and both main bronchi. Sections taken from the stoma or tracheal incision were considered separately. Statistical analysis was by analysis of variance and Student's *t* test.

RESULTS

Epithelial Loss. The extent and severity of loss of epithelium for each study group are shown in Table 1.

Whereas following tracheotomy significant epithelial loss occurred in the region of the tube tip, intubation resulted in loss more proximally, at the carina and in the main bronchi.

Ventilated animals in general had an increase in epithelial loss when compared to nonventilated animals, which had identical airway bypass but

TABLE 1. EPITHELIAL LOSS (MEAN±SE)

Experimental Group	*No. of Sections*	*% Minor* Loss*	*% Major* Loss*	*Total % Loss*
Carina and bronchi				
Intubation	14	18.0±6.4	16.8±3.6†	34.9± 7.4†
Tracheotomy	9	22.0±8.0	0.8±4.5	22.8± 9.2
"Sham" tracheotomy	6	7.6±9.7	7.4±5.5	15.0±11.3
Control	6	0.0	4.7±5.5	4.7±11.3
Trachea (around tube tip)				
Intubation	13	12.0±3.4	11.9±7.1	23.9± 8.0
Tracheotomy	9	5.8±4.1	48.2±8.5†	54.1± 9.7§
"Sham" tracheotomy	2	4.7±8.7	0.0	4.7±20.5
Control	2	0.0	0.0	0.0

*See text for definitions.

†p<.05 versus control group (ANOVA).

§p<.01 versus control and "sham" groups (ANOVA).

breathed unaided. However, this difference only achieved statistical significance for loss of cilia (Table 2).

Submucosal Inflammation. The extent of submucosal inflammation is recorded in Table 3.

Intubation induced a significant inflammatory response at all levels, the extent being greater in the proximal tracheobronchial tree than around the tube itself. Tracheotomy, however, did not result in significant changes in the proximal airway, and inflammation in the trachea was hardly greater than that seen following "sham" tracheotomy, in which there was a surgical procedure but no upper airway bypass.

The introduction of ventilation significantly increased the amount of submucosal inflammation identified around the tube tip (Table 4).

This study did not attempt to quantify the severity of submucosal inflammation, but it was observed that at some sites there was marked penetration of acute inflammatory cells through the mucosa and into the lumen of the airway (Fig 3D). This occurred adjacent to more severe submucosal inflammatory change.

At the stoma, tracheotomy and "sham" tracheotomy both resulted in a considerable degree of major epithelial loss and inflammation. There were no data to suggest that the presence of a tube for 1 hour exacerbated the traumatic effect and inflammatory response induced by the surgery alone.

Hemorrhage. Submucosal hemorrhage was largely confined to the level of the stoma, and was significant only for animals who had tracheotomies (Table 5).

DISCUSSION

TABLE 2. EPITHELIAL LOSS (MEAN±SE) FOR VENTILATED VERSUS NONVENTILATED ANIMALS

Experimental Group	*No. of Sections*	*% Minor* Loss*	*% Major* Loss*	*Total % Loss*
Carina and bronchi				
Ventilated	12	33.5±9.4§	6.5 ± 2.6	39.9± 9.9
Nonventilated controls	11	4.5±2.4	15.0± 6.3	19.4± 8.3
Trachea (around tube tip)				
Ventilated	12	13.9±4.6	32.6±10.3	46.5±10.4
Nonventilated controls	10	4.3±1.8	19.7± 8.4	24.0± 8.3

*See text for definitions.

†p<.01 versus controls (*t* test).

The present study investigates the acute response of the respiratory epithelium to upper airway bypass, and attempts to differentiate the specific histopathologic consequences of endotracheal intubation, tracheotomy, and mechanical ventilation. Experimental studies suggest that the respiratory tree is markedly sensitive to even minimal direct trauma.[9] In clinical practice this sometimes results in subglottic or tracheal stenosis,[10] but even edema alone can cause narrowing, notably in intubated neonates.[11] This important complication may be life-threatening and can occur following brief intubations for anesthesia.[8] Fewer data are available on the more proximal epithelial sequelae of upper airway bypass. Though in clinical, animal, and autopsy studies, other investigators have reported proximal tracheal and bronchial erosions and inflammation after intubation,[12-15] these have been largely attributed to bronchial placement of the endotracheal tube or trauma from suctioning. The present study highlights other factors that may be involved.

The results reported in this paper suggest that as little as 1 hour of nonhumidified air through an endotracheal tube can cause significant epithelial damage in the main bronchi and carina. These sites were well distanced from any direct traumatic effects that could be attributed to impingement of the tube itself. All tube placements in this study were controlled and uncomplicated, all animals were fully anesthetized and did not move during the experi-

TABLE 3. SUBMUCOSAL INFLAMMATION (MEAN±SE)

Experimental Group	*No. of Sections*	*% Edematous Only*	*% Edematous With Inflammatory Cells*
Carina and bronchi			
Intubation	14	57.6± 6.5*	71.3± 6.8*
Tracheotomy	9	19.1± 8.1	46.0± 8.5*
"Sham" tracheotomy	6	13.9±10.0	20.6±10.4
Control	6	3.1±10.0	3.9±10.4
Trachea (around tube tip)			
Intubation	13	54.1± 7.5	63.6± 7.2†
Tracheotomy	9	44.9± 9.0	64.3± 8.6§
"Sham" tracheotomy	2	41.2±19.0	41.4±18.3
Control	2	0	1.3±18.3

*p<.001 versus control group.

†p<.05 versus control group.

§p<.05 versus control group, but p>.05 versus "sham" controls.

TABLE 4. SUBMUCOSAL INFLAMMATION (MEAN±SE) FOR VENTILATED VERSUS NONVENTILATED ANIMALS

Experimental Group	*No. of Sections*	*% Edematous Only*	*% Edematous With Inflammatory Cells*
Carina and bronchi			
Ventilated	12	46.2±10.2	72.0±7.8
Nonventilated controls	11	38.6± 9.7	49.9±9.5
Trachea (around tube tip)			
Ventilated	12	49.1± 7.1	73.1±5.2*
Nonventilated controls	10	40.2± 7.1	52.8±7.8

*p<.05 versus controls (*t* test).

TABLE 5. SUBMUCOSAL HEMORRHAGE (% OF CIRCUMFERENCE: MEAN±SE)

Experimental Group	*Stoma*		*Trachea Around Tube Tip*		*Carina/Bronchi*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Intubation	0	0.0	13	0.7±3.7	14	2.0±2.0
Tracheotomy	3	55.6±7.7*	9	5.0±4.5	9	0.0
"Sham" tracheotomy	2	0.0	2	0.0	6	0.0
Control	0	0.0	2	0.0	6	6.5±3.0

*p<.001 versus all groups (ANOVA).

ment, and no tube was close to the carina at immediate autopsy. Intubation also caused submucosal inflammation in the proximal airway, the extent of the inflammatory response being greater in the bronchi than adjacent to the tube tip. The proximal effects of tracheotomy were considerably milder than following oral intubation, and the extent of injury at the carina and main bronchi was not greater than occurred following "sham" tracheotomy. The detrimental effects observed after tracheotomy were, by and large, concentrated in the region of the tube tip, and were assumed to be a consequence of direct trauma.

In a previous study, intubation of fetal lambs for 3 to 9 hours resulted in a third of the proximal tracheal epithelium's being eroded, while animals undergoing tracheotomy developed less extensive mucosal loss.[5] As in the present study, direct trauma was excluded, though the damage may have been influenced by ventilation using 100% oxygen. The effects of tracheotomy on the carina and bronchi have been studied after 18 to 72 hours in beagle puppies, and while epithelial damage and submucosal inflammation were evident at 18 hours, there appeared to be some resolution of squamous metaplasia after 36 hours.[6] Other experiments have shown inflammation and erosions occurring in the main bronchi and carina of anesthetized cats ventilated conventionally for 8 and 16 hours via endotracheal tubes.[16,17] In these studies a neonatal heated humidity system was incorporated, but no control data were reported. All of these studies support the concept that indirect harm to the proximal airway is a feature of artificial airway management, but they also highlight the complex combination of factors involved.

To explain the severity of carinal and bronchial damage, it is necessary to analyze the known consequences of upper airway bypass more closely. Variations in humidity have been shown to decrease mucociliary function, and extreme dryness causes cellular damage.[2] Similar responses are seen to alterations in temperature.[3] These factors were not controlled in this study, but it is probable that they contributed to the histologic changes recorded. Bypass of the nasopharynx leads to the loss of its purifying function. Inspiration of exogenous irritants such as cigarette smoke, ammonia, or sulfur dioxide[4] can cause mucosal damage, though none of these agents played a role in this experiment. Impairment of respiratory mucosal function has been reported as a consequence of certain anesthetic agents,[18] variations in inspired oxygen concentration,[19] and direct contact of the epithelium with blood or serum.[20]

In the present study all animals breathed room air; the presence of hemorrhage did not correlate to the degree of histologic damage. Instrumentation of the trachea may be complicated by the introduction of bacteria,[21] and in studies of intubated patients this has been shown to be an early consistent finding.[22] The disturbance of mucociliary function caused by other factors may be enough to allow this contamination to impact adversely upon the bronchial mucosa. Bacterial tracheitis is a reported complication of intubation,[23] though for this to occur within 1 hour is improbable. Gastroesophageal reflux with the aspiration of gastric acid can also predispose to tracheal stenosis[24] — occult acid reflux could conceivably have occurred in the anesthetized rabbits. The influence of an endotracheal as opposed to a tracheotomy tube on the proximal flow of acidic luminal fluid from the epiglottis is open to conjecture, though it is generally considered (possibly inaccurately) that either tube protects the trachea from aspiration.

The observation that endotracheal intubation is more damaging to the main bronchi than tracheotomy may be explained by the effects of altered air currents on the respiratory epithelium. Hilding[25] demonstrated squamous metaplasia in response to increased airflow in the nasal turbinates of rabbits and dogs, and this phenomenon is also observed in the respiratory epithelium of postlaryngectomy patients.[26] Autopsies of human neonates have linked respiratory epithelial injury to high-frequency jet ventilation,[27] and experimental studies have shown epithelial erosions following 16 hours of high-frequency ventilation in cats.[17] The reduction in dead space after tracheotomy (in comparison to an endotracheal tube) is accompanied by a reduction in tidal volume requirement, inspiratory flow rate, and pressures. The drying effect during inspiration will be strongly influenced by the tidal flow rate and pressures, and thus tracheotomy might be expected to cause less mucosal desiccation than intubation. The (minor) increases in damage seen after ventilation may also be attributed to the increased pressures and flow rates needed for ventilation through an endotracheal tube.

The relevance of these results to clinical practice is evident. Prolonged intubation may not be a prerequisite for complications to occur.[10] The need to attend to the nasopharyngeal functions of humidification, warming, and purification as soon as possible after establishing an airway is important. In controlled situations such as the induction of anesthesia, this detail is observed, but in emergencies or during patient transport the situation may be different. This study also has some bearing on the surprising resistance of long-term tracheotomy patients to respiratory complications. Certainly an ambulatory tracheotomy subject, especially in infancy, is at risk for respiratory tract infections, obstruction with mucous plugs, and tube displacement. However, chronic lack of humidification and warming of inspired air might be expected to cause considerably more debility than they often do.[28] Furthermore, this study points to a potential risk in combining high-flow ventilation techniques with inadequate humidification of inspired gas, a combination already implicated in the pathogenesis of a rare but dangerous neonatal condition, necrotizing tracheobronchitis.[27]

Finally, the present study describes a technique for quantifying histologic changes in epithelial surfaces, using a method that could be applied to other clinical or experimental studies in which the data require microscope evaluation. For experimental research into tracheal disease, we can recommend the rabbit model despite the paucity of previous reports. The relatively long trachea lends the animal well to studies of the complications of airway management; the size match and brisk inflammatory response are particularly appropriate for correlation with the neonate, and experimental studies have highlighted the microanatomic similarities between human and rabbit tracheas.[29] Furthermore, rabbits are less expensive and easier to keep than the more traditional canine model.

In conclusion, the data reported from this experiment should alert clinicians to the indirect consequences of nasopharyngeal bypass, especially endotracheal intubation.

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Ann Otol Rhinol Laryngol 99:1990

ROLE OF ANGIOGRAPHY IN THE MANAGEMENT OF REFRACTORY EPISTAXIS

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When interruption of the related arteries fails to control epistaxis, angiography is recommended for identification of the vascular base, the collateral circulation, and the possibility of arterial abnormalities. Criteria are proposed for utilization of vascular mapping, and relevant cases are cited to support the specific indications for application.

KEY WORDS — angiography, epistaxis.

Uncontrolled epistaxis may require arterial ligation for hemostasis. The goal of this paper is an identification of those circulatory disorders that impact upon the surgical control of life-threatening hemorrhage. Through an analysis of appropriate cases supported by carotid artery angiography, specific guidelines are proposed for identification of collateral circulation to the nose and, based upon this information, the potential location for arterial interruption. Criteria for angiography are suggested, and contraindications to arterial ligation are identified by angiographic analysis.

HISTORICAL REVIEW

The importance of the craniofacial arterial circulation, and specifically that of the nasal chamber relevant to epistaxis, is emphasized in the review of the following clinical and radiologic literature.

The collateral circulation of the orbit and the secondary flow to the nose and the anastomoses between the internal carotid artery (ICA) and the external carotid artery (ECA) were described by Soemmerring[1] (1818), DuBrueil[2] (1847), and Meyer[3] (1887) and in many reports of more recent vintage. Anastomoses between the ECA through the facial, maxillary, and temporal arterial branches and the ICA divisions of the ethmoidal, periorbital cutaneous, and ophthalmic arteries are the major connections between these arterial systems. Lasjaunias et al[4,5] identified the factors of "congenital disposition" (ie, developmental), vascular constraints (ie, pathologic states), and the interaction of these factors upon the hemodynamic possibilities of collateral circulation. They observed that the major anastomotic system between the ECA and ICA is the internal maxillary artery (IMA) pattern, which may resupply the brain following ICA occlusion beyond the capability of other channels. The complex circulation of the proximal and distal IMA is depicted comprehensively in the text entitled *Craniofacial and Upper Cervical Arteries* by the same author.[4] The importance of the ascending pharyngeal, the facial, the transverse facial, and the ICA components to the IMA pattern is stressed. Following IMA occlusion the facial artery becomes the major source of collateral circulation via the buccal and infraorbital arterial branches. Unfavorable congenital dispositions for unilateral collateral circulation include a hypoplastic facial artery with internal maxillary dominance, and a middle meningeal origin from the ophthalmic artery. In addition to the inconsistent regional collateral pattern, vascular malformations and aberrant arterial structures exaggerate the variability of the craniofacial circulation.

The ophthalmic artery circulation, while normally a branch of the ICA, may be supplied by the ECA system because of pathologic conditions such as progressive stenosis or total occlusion of the ICA.

Huckman and Haas[6] described two cases with angiographic support of reversed ophthalmic artery flow due to ipsilateral occlusion of the ICA with shunting through the dilated ophthalmic artery from the ECA. DeChiro[7] and Mount and Taveras[8] identified the role of the circle of Willis as a source for ophthalmic circulation in the event of ICA stenosis and point to the importance of the collateral circulation (ECA system) in the situation of an inadequate anterior communicating artery.

From a clinical standpoint, advances in vascular surgery supported by angiography have identified many individuals with either unilateral or bilateral ICA insufficiencies due to stenosis or occlusion. In these instances, further compromise of the collateral flow by ligation of the ECA system may result in visual impairment due to inadequate ophthalmic circulation. Additionally, intracerebral damage due to inadequate collateral flow via the network of the ophthalmic artery, the carotid system, and the cerebral vessel axis may result from inopportune ligation.

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Prior to the description of internal maxillary ligation by Seiffert[9] (1928) and Gergely[10] (1935), the mainstay of surgery for severe epistaxis was ECA ligation. These authors recognized the failure rate of ECA ligation to be unacceptably high and instead attacked branches of the artery toward the bleeding site. Subsequently, in 1965, Chandler and Serrins[11] emphasized the value of IMA ligation, which has become the primary procedure for intractable epistaxis. The rate of failure of simple packing was described as approximately 25%,[12] while Wang and Vogel[13] reported a 14% failure rate of IMA ligation; similarly, on review of the last 100 cases, we identified a 5% recurrence rate of epistaxis.

CLINICAL APPLICATION

Having recognized the anatomic factors involved in the nasal circulation, and the clinical fact that regional arterial ligation is not always successful (5% to 14%), we reviewed the literature and our cases to determine causes for delayed or continued hemorrhage. We were able to identify the following four factors:

1. Dominant collateral flow from the ipsilateral facial and meningeal arteries.
2. Delayed development of compensatory collateral expansion and recirculation to the bleeding site.
3. Anatomic variation of the posterior nasal and pharyngeal arteries from the IMA.[14]
4. Technical features such as arterial clip slippage, failure to properly identify the related IMA, or inadequate ligation of the IMA.[15]

There are some compensatory adjustments that may alleviate regional arterial obstruction: 1) the presence and competence of the collateral circulation, and 2) the location of the arterial interruption with respect to the proximal point of origin or distally to the region of terminal arterial perfusion. The presence or absence of these compensatory anatomic factors is illustrated in the following cases, and therapeutic decisions were based upon this information.

CASE REPORTS

PROXIMAL EXTERNAL CAROTID ARTERY LIGATION

Case 1. A 68-year-old hypertensive man underwent ECA ligation for uncontrolled epistaxis prior to popularization of the IMA technique. This procedure successfully controlled the problem until approximately 1 year later, at which time a major hemorrhage was ultimately controlled by transantral ligation of the related IMA system. During the succeeding 10 years there was no further difficulty with epistaxis. At the second operation, on removal of the posterior sinus plate, a massive collateral network of dilated and vigorously pulsating arteries was visualized, and because of their markedly increased diameter these vessels were clipped with considerable difficulty. On comparison with subsequent cases in which the IMA could be measured directly, the compensatory dilatation was observed to be in the range of threefold to fourfold greater than the normal arterial diameter.

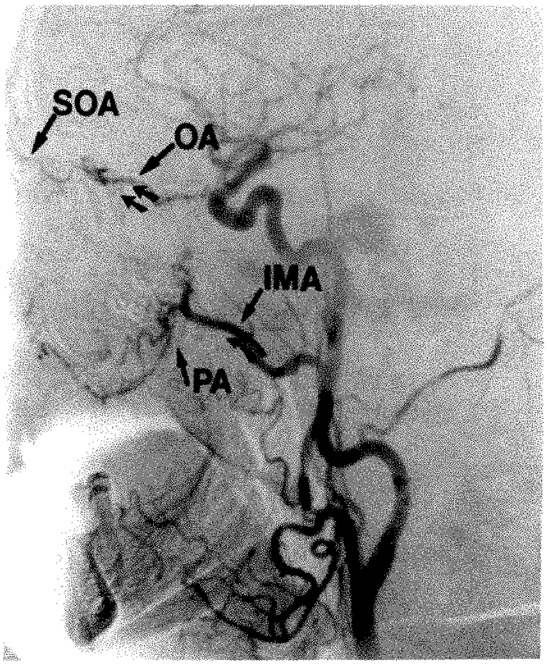

Fig 1. (Case 2) Subtraction angiogram of carotid vessels demonstrating normal direction of flow indicated by arrows along internal maxillary artery (IMA) and ophthalmic artery (OA). Nasal circulation is interrupted by clips on IMA in pterygoid space. SOA — supraorbital artery, PA — palatine artery.

TRANSANTRAL INTERNAL MAXILLARY ARTERY LIGATION

Case 2. This 66-year-old insulin-dependent hypertensive man underwent left IMA ligation 14 months prior to the current admission for recurrent ipsilateral posterior epistaxis. A selective angiogram was employed to identify the integrity of the previous ligation, the collateral flow, and, when possible, the bleeding site. In Fig 1, the arterial clips are obviously effective, since the nasal circulation is interrupted while the regional branches of the laterally originating palatine vessels are patent. The ophthalmic artery originating from the siphon of the ICA is visualized. The ethmoidal and septal arteries appear as a fine vessel blush superimposed upon the nasal profile. The study does not identify a bleeding point at the time of angiography.

INTERNAL CAROTID ARTERY OCCLUSION, RETROGRADE OPHTHALMIC CIRCULATION FROM EXTERNAL CAROTID ARTERY

Case 3. This 56-year-old woman underwent a neuroradiologic investigation for transient motor weakness of the left arm and leg. The patient denied visual disturbances and sensory impairment. A

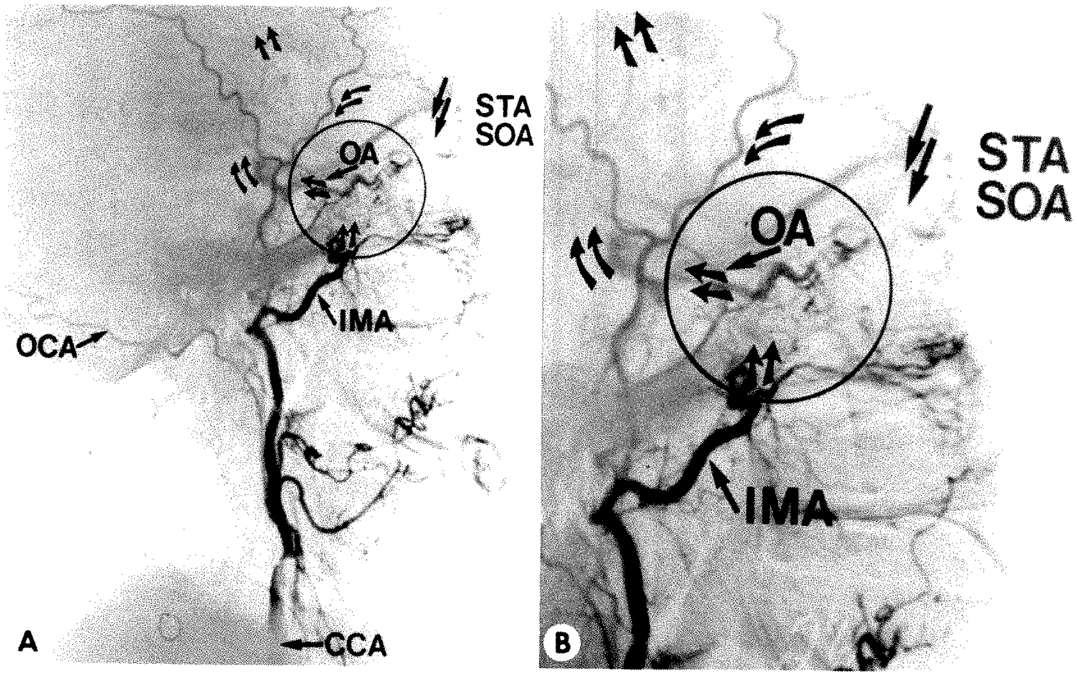

Fig 2. (Case 3) A) Total stenosis of internal carotid artery at bifurcation of common carotid artery (CCA). External carotid artery is patent; direction of flow is retrograde to ophthalmic artery (OA) via internal maxillary artery (IMA) branches, supraorbital artery (SOA), and supratrochlear artery (STA). OCA — occipital artery. B) Magnified orbital circulation emphasizing collateral network filling OA by retrograde flow.

selective right carotid angiogram demonstrated total occlusion of the ICA with normal patency of the branches of the ECA (Fig 2A). By sequential radiographs the flow pattern of the ophthalmic artery was observed to occur via the periorbital cutaneous anastomoses, through a retrograde flow into the patent siphon of the ICA, and subsequently to the anterior and middle cerebral arteries (Fig 2B). The nasal circulation is not modified, though on comparison with other carotid angiograms the IMA appears to be relatively dilated.

Case 4. This 76-year-old man was evaluated for syncopal attacks, transient bouts of light-headedness, and occasional weakness of the left arm and leg associated with peripheral paresthesias. The results of the neurologic examination were within normal range. The angiogram demonstrated total occlusion of the right ICA with some narrowing at the origin of the ECA, and competent peripheral branches, including the IMA (Fig 3). Subsequent films revealed retrograde flow into the ophthalmic artery through the orbital anastomoses. The fine vascular blush over the orbital contents reveals the anastomotic network.

INTERNAL CAROTID ARTERY STENOSIS AND OPHTHALMIC ARTERY OCCLUSION

Case 5. This 74-year-old man was evaluated for intermittent episodes of vertigo and occasional bouts of nose bleeding. Several years before this examination the patient had undergone a right cataract extraction, 2 days following which blindness occurred. The current investigation included an angiogram that demonstrated severe stenosis of the right ICA at the carotid bifurcation and adequate filling of the cerebral circulation (Fig 4). The ophthalmic artery could not be identified in this

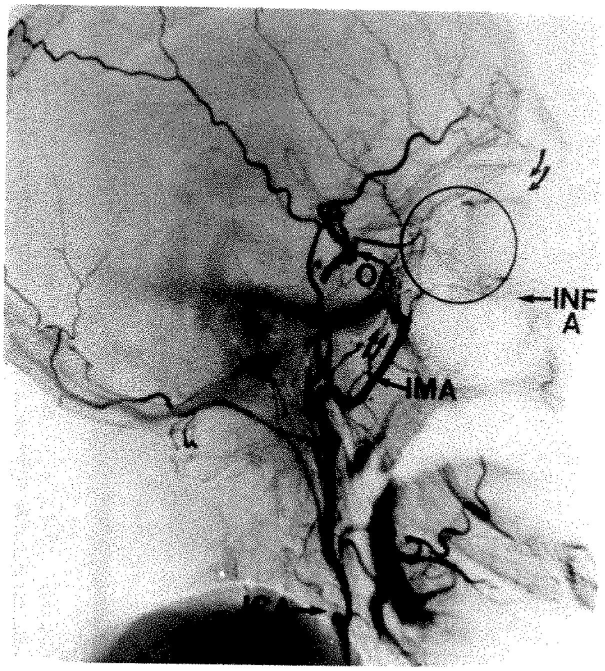

Fig 3. (Case 4) Angiogram illustrating total occlusion of internal carotid artery (ICA) above bifurcation of common carotid artery. Ophthalmic artery (OA) derives circulation by retrograde flow from terminal arteries of external carotid artery and collateral vessels of internal maxillary artery (IMA). In turn, siphon and cerebral circulation are supplied by anastomotic orbital network (encircled). INF A — infraorbital artery.

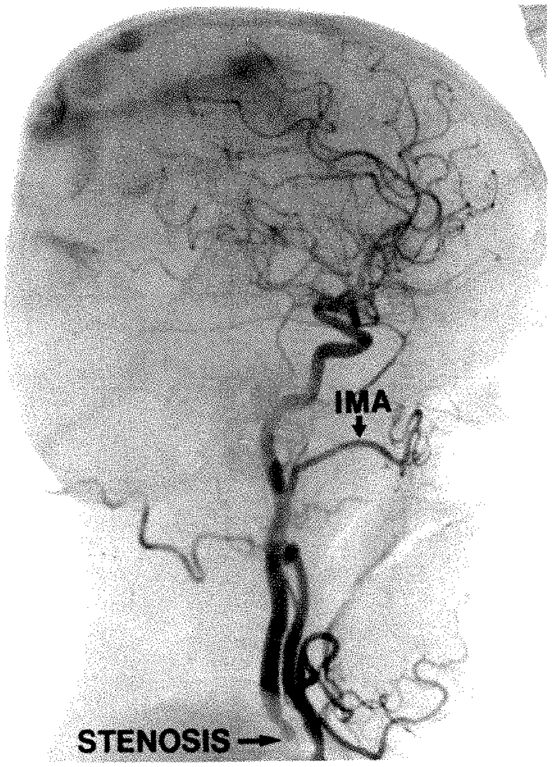

Fig 4. (Case 5) Carotid angiogram illustrating stenosis of right internal carotid artery and adequate filling of cerebral circulation. Ophthalmic artery is not visualized; internal maxillary artery (IMA) and associated branches are patent.

study. Sequential films depicted the normal ECA anatomy and circulation.

BILATERAL INTERNAL ARTERY STENOSIS WITH CEREBRAL CIRCULATION FROM EXTERNAL CAROTID ARTERY AND VERTEBRAL-BASILAR SYSTEMS

Case 6. This 68-year-old woman was examined for persistent headache following trauma sustained in a vehicular accident. Surprisingly, in view of the findings on the subsequent angiogram, she had no neurologic complaints except for cephalgia. A computed tomograph of the head was normal except for cortical atrophy. The arterial study was suggested on the basis of barely palpable carotid artery pulsations and a grossly diminished Doppler ultrasound flow pattern. The angiogram was carried out by femoral route with selective arch flow and demonstrated ICA stenoses bilaterally (Fig 5). The vertebral artery, while patent, was distorted and stenotic; the ECA system was noted to be competent. The intracranial circulation was derived from the ECA collaterals and basilar artery via the circle of Willis.

DISCUSSION

The major thrusts of this article are a recognition of the causes of failure and the prevention of potential untoward sequelae due to surgical interruption of the nasal vasculature. The authors suggest that when angiography identifies significant vascular impairment of the ICA system, the ECA and the more proximal IMA ligation be deferred pending the application of other techniques for hemostasis. A second derivative of this study is an awareness that an additional compromise that is superimposed upon preexistent insufficiency of the central cerebral pattern and ophthalmic artery by ECA and/or IMA ligation may result in major neurologic and visual deficits.

The cases include both complex epistaxis problems and nonbleeding vascular diseases that would impact upon the selection of surgical intervention. The occasional futility of ECA ligation is emphasized by case 1. Compensatory collateral engorgement results, which compounds the challenge of arterial ligation.

Case 2 identifies total interruption of the terminal nasal branches of the IMA and filling of the palatine artery. The point of origin of this vessel is sufficiently lateral to be beyond the surgical field.

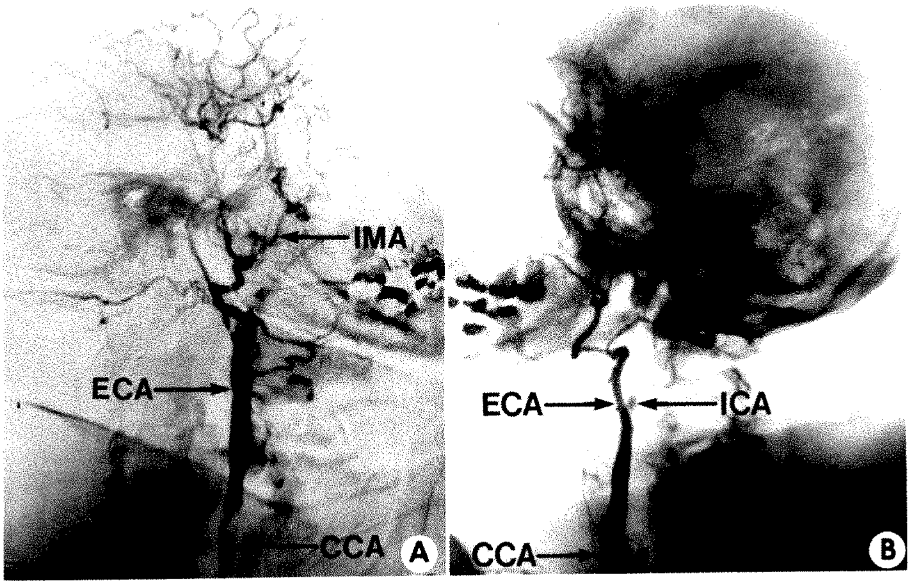

Fig 5. (Case 6) A) Subtraction study of right common carotid artery (CCA) system with total stenosis of internal carotid artery. Patency of external carotid artery (ECA) and branches is evident in this study. IMA — internal maxillary artery. B) Total occlusion of left internal carotid artery (ICA) and patency of ECA system.

Whether it contributes sufficient collateral flow to be significant is uncertain. The angiogram excludes congenital arterial variations and contralateral contribution to flow; consequently, further exploration of the pterygopalatine space is unnecessary. The significance of the ethmoidal arteries again is questionable, since the bleeding site appears to be within the posterior nasal chamber, though not well defined beyond this general location. The surgical therapy for continued bleeding would be followed by ECA ligation or, as available, selective IMA embolization.

Cases 3 and 4 and several others that are similar in pattern and clinical presentation indicate the importance of the ECA flow to the cerebral vasculature by the collateral channels in the presence of serious ICA incompetence or occlusion. Since the angiogram clearly defines the retrograde flow from the ECA (via IMA, etc) into the carotid siphon, ECA and/or IMA ligation are contraindicated for epistaxis because of the high probability of blindness and/or cerebral infarction.

The importance of case 5 is recognition of preexistent blindness due to vascular disease prior to arterial ligation. Identification and documentation of this disability cannot be overly stressed at this time.

Case 6 cites the possibility of survival with relatively few symptoms due to bilateral ICA stenosis when the remaining craniofacial circulation can develop sufficient collateral flow to accommodate the intracranial demand. Surgery that might impair the collateral source of the ECA, such as neoplastic resection or epistaxis control, could possibly diminish the cerebral flow to a level below the minimal flow requirements.

On the basis of the presented cases and others similar in type, degree, and location of vascular impairment, we recommend angiography prior to arterial ligation under the following circumstances:

1. Failure to control hemorrhage following adequate ligation of the IMA.
2. Identification of the ipsilateral regional circulation, eg, facial and meningeal arteries, and their individual contribution to the nasal circulation.
3. Evidence of collateral flow from the contralateral carotid system.
4. History (transient ischemic attack or cerebrovascular accident) or physical evidence (muscular paresis or paralysis) of carotid artery disease suggesting vascular impairment.
5. Vascular compromise of the globe (amaurosis fugax, ophthalmic artery occlusion with resulting blindness).

THERAPEUTIC PLAN

If the IMA ligation has been accomplished satisfactorily and the bleeding continues, the therapeutic plan is contingent upon identification of the collateral circulation at that time by the regional angiogram. If the vascular pattern suggests a significant contribution by the facial artery, then the primary target is this artery in conjunction with an ECA ligation. Other, less accessible collateral sources such as the meningeal artery may not be approached directly, and alternatives such as arterial embolization[16] with subsequent occlusion may be the remaining option for control. In our experience (three individuals) staged bilateral IMA ligation has not been successful.

Finally, identification of the collateral circulation that contributes to the nasal chamber has been described in detail. The risk of regional damage due to a latent circulatory inadequacy exaggerated by interruption of the collateral circulation was emphasized, and the methods of secondary control were reviewed and recommended to be used as the individual situation demands.

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EVALUATION OF AMINO-OXYACETIC ACID AS A PALLIATIVE IN TINNITUS

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Amino-oxyacetic acid (AOAA) was evaluated as a palliative in tinnitus. Sixty-six patients with tinnitus presumed to be of cochlear origin were given either a placebo or 75 mg of AOAA four times a day for 1 week. Response was evaluated by both audiometric measurement of tinnitus loudness and subjective rating by patients of change or no change in tinnitus severity. Because loudness measurements and self-rating have not been shown to be independent, and since the aim of clinical treatment of tinnitus is the alleviation of subjective distress, greater weight was given to the patient's self-rating. A total of 21% of all patients reported a subjective decrease in tinnitus severity, usually within 3 to 4 days after the start of AOAA use. Patients with tinnitus caused by presbycusis or Meniere's disease were the most likely to respond to AOAA treatment with a reduction in tinnitus severity, whereas those with drug-induced tinnitus were the least likely to respond. Nausea and dysequilibrium were the most common side effects of AOAA use. Of the 21% of patients who responded to AOAA, 71% developed some type of side effect. Amino-oxyacetic acid produces a reduction in the severity of tinnitus in about 20% of patients; however, the incidence of side effects makes the drug unacceptable for clinical use.

KEY WORDS — amino-oxyacetic acid, drug treatment, tinnitus.

INTRODUCTION

Amino-oxyacetic acid (AOAA) is known primarily as an inhibitor of the catabolism of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). As such, it was given clinical trial as an anticonvulsant in the 1960s.[1,2]

In our laboratory, AOAA was used in research designed to test whether GABA was involved in cochlear function.[3] In the course of that research we discovered that AOAA produced a completely reversible short-lasting transient hearing loss in guinea pigs.[4] Bobbin et al[5] then demonstrated that AOAA caused a reduction in the endocochlear potential (EP), and it was believed that this reduction might be responsible for the transient hearing loss.

The relationship between a reduction in the EP and a reduction in spontaneous eighth nerve firing rates was demonstrated convincingly by Sewell.[6] The relationship between tinnitus and an elevated eighth nerve firing rate has not been proven conclusively, but Evans et al[7] found elevated firing rates in the eighth nerves of animals treated with high doses of aspirin, and Jastreboff and Sasaki[8] found increased neural activity in the inferior colliculi of aspirin-treated animals. Sasaki et al[9] found an increased uptake of 2-deoxy-D-glucose, indicative of increased neural activity, in auditory structures after auditory deafferentation, which, they report, often results in tinnitus. Therefore, we reasoned that if tinnitus is associated with increased afferent activity and reduction of the EP is correlated with reduction in afferent activity, then a drug such as AOAA, which suppresses the EP and has been shown to be clinically tolerable, is a good candidate for trial in tinnitus management. A preliminary, small-scale clinical study of AOAA in tinnitus produced results that encouraged us to study the use of AOAA in a large population of patients with tinnitus presumed to be of cochlear origin but due to various causes.

MATERIALS AND METHODS

The patients were women without child-bearing potential, and men. They were chosen from among private patients or Veterans Administration patients who reported severe tinnitus, or from people responding to radio, television, and newspaper advertisements.

The patients were screened and those with hepatic disorders (including alcoholism); cardiac, gastrointestinal or convulsive disorders; or mental incompetence were eliminated from the study. Patients who passed this screening underwent a complete medical history and physical examination. Accepted patients were given intravenous lidocaine hydrochloride (1 to 2 mg/kg over a 3- to 4-minute period) to determine whether they were lidocaine-positive (ie, lidocaine caused a reduction in tinnitus intensity) or lidocaine-negative. This was done because it had been reported that lidocaine was effective in reducing tinnitus associated with cochlear disease.[10] Electrocardiographic monitoring was car-

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TABLE 1. AMINO-OXYACETIC ACID RESPONSE FOR LIDOCAINE-POSITIVE AND -NEGATIVE PATIENTS

Lidocaine-positive (n = 56)			
AOAA-responsive	11	11/56	(20%)
AOAA-responsive with side effects	8	8/11	(72%)
AOAA-responsive and nonresponsive with side effects	17	17/56	(30%)
Lidocaine-negative (n = 10)			
AOAA-responsive	3	3/10	(30%)
AOAA-responsive with side effects	2	2/ 3	(67%)
AOAA-responsive and nonresponsive with side effects	3	3/10	(30%)
Total patients (n = 66)			
AOAA-responsive	14	14/66	(21%)
AOAA-responsive with side effects	10	10/14	(71%)
AOAA-responsive and nonresponsive with side effects	20	20/66	(30%)

AOAA — amino-oxyacetic acid.

ried out during lidocaine infusion. The patients completed the questionnaire of the American Tinnitus Association, and reported to the pathology laboratory for a complete blood count, SMA 12/60 ([Sequential Multiple Analyzer] tests for glucose, urea nitrogen, calcium, uric acid, albumin, total protein, inorganic phosphorus, creatinine, total bilirubin, aspartate aminotransferase, alkaline phosphatase, and cholesterol), urinalysis, and a test for stool occult blood.

If the laboratory test results were within normal values, the patients were evaluated audiometrically with pure tone audiometry at conventional and ultrahigh frequencies; speech audiometry including speech reception threshold, speech recognition scores, and tinnitus-matching for pitch and loudness; the short increment sensitivity index; and tone decay. Impedance and acoustic reflex testing were administered at the initial session to assist in determining the site of the lesion only. Patients with Meniere's disease also were tested by electronystagmography (ENG). Patients were requested to stop using nonsteroidal anti-inflammatory agents, antivertigo medications or antibiotics, or tinnitus maskers during the 21-day experimental protocol period.

Sixty-six patients with tinnitus were divided into seven groups according to the following criteria.

1. Sudden hearing loss and lidocaine positivity.
2. Noise-induced hearing loss and lidocaine positivity.
3. Presbycusic hearing loss and lidocaine positivity.
4. Drug-induced hearing loss and lidocaine positivity.
5. Meniere's disease and lidocaine positivity.
6. Traumatic hearing loss and lidocaine positivity.
7. Tinnitus presumed to be of cochlear origin and lidocaine negativity.

Tinnitus was presumed to be of cochlear origin if the results of audiometry, including site-of-lesion tests, and medical history and physical examination did not reveal evidence of either conductive or retrocochlear involvement and the response to lidocaine was positive. The deciding factor was medical diagnosis. As pointed out by Shailer et al,[11] because we were audiometrically selecting subjects with cochlear hearing loss and medically screening for cochlear diseases (eg, medical diagnosis), patients selected ultimately could be presumed to have tinnitus of cochlear or sensorineural origin.

Patients then were given either placebo capsules or AOAA capsules (75 mg/capsule) at random, to be taken one capsule four times a day for 7 days. On day 7 patients were evaluated by medical history and physical examinations, and audiometric and pathology laboratory examinations as described above. From days 7 to 14 no capsules were taken, but on day 14 the same evaluation as on day 7 was made. From days 14 to 21 patients were given either placebo or AOAA capsules, depending on which they had taken earlier, to complete the random crossover design. On day 21 another complete evaluation as on day 7 was made. All evaluations were made double-blind. We monitored patient capsule-taking compliance by collecting the vials at the end of the 21-day protocol and counting remaining capsules.

Patients also were given a tinnitus subjective rating scale and were asked to rate their tinnitus severity twice a day for the 21 days on a scale of 1 to 10 (1 being no tinnitus at all and 10 being the worst they could imagine). In addition, patients were given a subjective rating scale to take home after the 21-day protocol, to be returned by mail. However, very few patients returned these rating scales. Some patients were contacted by telephone to determine the postprotocol status of their tinnitus.

RESULTS

Of the 66 patients in this study, 14 (21%) reported a subjective reduction in tinnitus in the week during which they took AOAA (Table 1). Only two patients (3%) reported a reduction in tinnitus while receiving the placebo. Table 2 indicates the incidence of positive response to AOAA use and the side effects, according to the cause of the tinnitus.

The only patients who had incidences of improvement while receiving AOAA greater than the incidence of the entire cohort of patients (14/66, 21%) were those with Meniere's disease (3/8, 37.5%) or presbycusis (3/11, 27%) and the lidocaine-negative group (3/10, 30%). Use of AOAA proved least efficacious in the group of patients with drug-induced tinnitus.

Patients with Meniere's disease represent a special group in that they had the greatest incidence and intensity of side effects while receiving AOAA — so much so that six had to drop out of the study before it was completed. The data from these six pa-

TABLE 2. AMINO-OXYACETIC ACID RESPONSE AND SIDE EFFECTS BY CAUSE OF TINNITUS

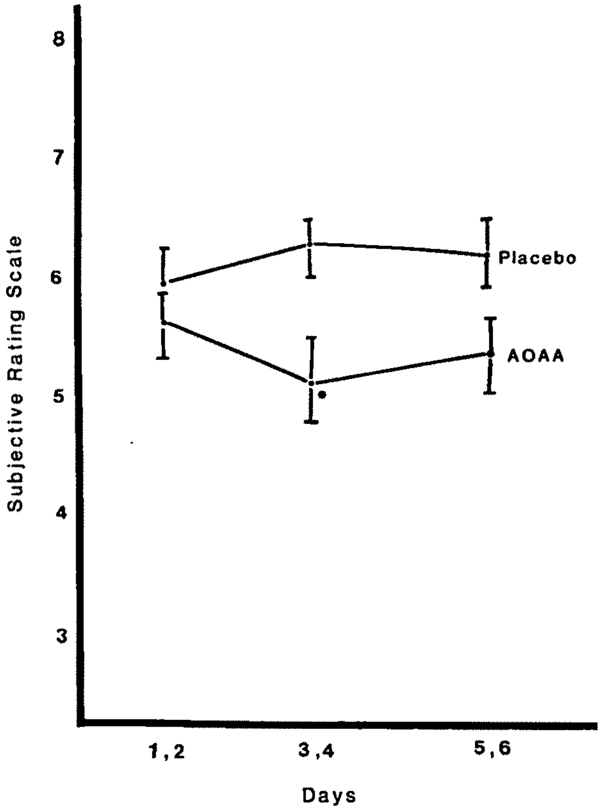
		AOAA-Responsive		*Side Effects When on AOAA*		*AOAA-Responsive With Side Effects When on AOAA*	
	No. of Pts	*No. of Pts*	*%*	*No. of Pts*	*%*	*No. of Pts*	*%*
Lidocaine-positive							
Sudden hearing loss	7	1	14	1	14	1	100
Noise-induced hearing loss	11	2	18	5	45	2	100
Presbycusis	11	3	27	3	27	1	33
Drug-induced hearing loss	8	0	0	5	63	0	0
Meniere's disease	8	3	38	3	38	2	66
Trauma	11	2	18	0	0	2	100
Lidocaine-negative	10	3	30	3	30	2	67

tients are not included in this report. Thus, the patients with Meniere's disease remaining in the study are those less sensitive to the side effects than was the group as a whole.

The side effects reported were nausea (20 patients), dysequilibrium or balance problems (12 patients), drowsiness (six patients), vomiting (five patients), and disorientation (one patient). Some patients suffered more than one side effect. In only one patient was the side effect incapacitating.

Twenty-six of the 66 patients had more than eight AOAA capsules remaining after the study had been completed. Despite this partial compliance, these data were included because there was no difference between the compliant and partially compliant groups in their responses to AOAA.

During the course of this study we found that most patients who reported reduction in tinnitus intensity while receiving AOAA exhibited a similar pattern of response to the drug. The general time pattern of response was no response for the first day or two, then a reduction in tinnitus for a few days, and side effects on the last days of the week. To verify the validity of our clinical impression, we compared patients' subjective ratings of their own tinnitus by examining groups of days from the AOAA week and the placebo week. The greatest difference was obtained when the means of days 3 and 4 from both weeks were compared. The mean subjective rating for patients receiving AOAA for days 3 and 4 was 5.1±0.41 (SEM) and for patients receiving placebo was 6.3±0.35 (SEM); this was significant by t test at the $p<.05$ level. Comparisons of the means of days 1 through 4 of the drug and placebo weeks, or the means of days 1 and 2 against days 3 and 4 in the two weeks, did not prove significant (see Figure). Interestingly, however, the mean of the subjective ratings of the AOAA-positive group for all 7 days while receiving AOAA (5.35±0.25 [SEM]) was significantly lower than the mean of this same group's placebo week rating (6.08±0.25 [SEM]) at the $p<.05$ level.



Average subjective rating scale during placebo or AOAA administration. Includes only patients responsive to AOAA. Asterisk — significantly different from placebo ($p<.05$), error bars — SEM.

On the basis of the clinical impression of a pattern to the therapeutic and side effects of AOAA, we started one group of six patients whose tinnitus was known to be reduced by AOAA on 75 mg four times a day for 2 days as a loading dose and continued the dosage at 37.5 mg four times a day for the remainder of the week to reduce the incidence and severity of side effects. None of these patients, all of whom tested positive while receiving a full dose of AOAA, reported a reduction in their tinnitus intensity while on this modified regimen.

Following is a list of variables taken from the tinnitus questionnaire, the patient's history, and the experience of this study that were compared and shown *not* to be correlated:

1. AOAA positivity versus relief with any other treatment.
2. Changes in audiometric measures (including tinnitus pitch and loudness matches) between AOAA and placebo weeks.
3. All pathology laboratory values remaining within normal limits.
4. AOAA positivity versus the patient's sex, age, or duration of tinnitus.

5. AOAA positivity versus lidocaine positivity.
6. Lidocaine positivity versus duration of tinnitus.

The effects of the lidocaine infusion were as reported elsewhere[6]: tremors, slurring of speech, lightheadedness, and confusion. One of our patients suffered transient global amnesia following lidocaine administration and was kept in the hospital under observation for a day without further difficulty.

DISCUSSION

Amino-oxyacetic acid first was used by us as a tool to uncover the possible role of the neurotransmitter GABA in cochlear function.[1] However, it seems unlikely that GABA is involved in the ability of AOAA to inhibit the EP,[5] which was the starting point of this investigation. γ-Aminobutyric acid is now thought to have some role in cochlear function,[12] but its nonuniform distribution would seem to preclude a role in the cochlea-wide phenomenon of the EP. There is little doubt that AOAA can act centrally as well,[13] and it may be that the inhibitory effect on tinnitus is mediated both peripherally and centrally. Likewise, the effect of lidocaine, thought by some to act primarily in tinnitus of cochlear origin,[10] is probably due to nonselective local anesthetic action in many areas of the CNS and the cochlea. The lidocaine-induced side effects, which involve several different CNS functions, support this notion. The fact that there is no correlation between AOAA positivity and lidocaine positivity may have many explanations (eg, pharmacokinetic differences between patients), but the most likely is that the two drugs probably are acting at different sites.

The change in the patients' own ratings of their tinnitus and their oral reports of improvement while receiving AOAA were the only significant changes seen in this study. The desired end result of therapy for tinnitus is the lessening of the patient's distress. Therefore, the patient's self-rating was given greater weight than the audiometric data. It should be emphasized that each patient served as his or her own control in this double-blind, placebo-controlled study. Also, the response to the placebo was only 3%. In our earlier study,[14] we reported improvements in speech discrimination scores while patients received AOAA therapy. This finding was not supported by the present study.

γ-Aminobutyric acid has been shown to have a role in central auditory processing.[15,16] Amino-oxyacetic acid may be exerting some of its antitinnitus effect by inhibiting the catabolism of GABA. It may be possible to enhance the inhibitory role of GABA in audition by combining AOAA with a GABA mimetic already in clinical use such as baclofen. This combination would have the added virtue of keeping the doses of each component low and thus reducing the incidence of side effects.

The time course of the effect of AOAA (ie, latency of several days) and the late appearance of side effects could be explained by a single phenomenon: the slow accumulation of AOAA in cochlear fluids. For example, it seems reasonable that a certain concentration of AOAA in cochlear fluids must be reached before the EP is depressed and tinnitus suppression results. This might be the "therapeutic window" concentration. As drug administration is continued and higher cochlear fluid concentrations are achieved, side effects, most of which can be attributed to the vestibular system, appear. The fact that Meniere's patients, more than any other group, dropped out of the study because of side effects also suggests that the side effects are of vestibular origin. The obvious answer to this problem is the pharmacokinetic one. Unfortunately, no satisfactory method for determination of AOAA in biologic fluids exists, and we were unsuccessful in our attempts to develop one. Knowledge of the pharmacokinetic parameters might permit alterations in dose and dosage interval that would avoid side effects.

The dose chosen (75 mg qid orally) was that used when AOAA was tried as an antiepileptic[1,2] and by us in its preliminary trial as an antitinnitus agent.[14] We conducted a very small-scale study in an attempt to arrive at the dosage least likely to cause side effects. Six patients, all of whom reported a reduction in their tinnitus at the full dosage, were asked to take the full dosage for 2 days (to "load" the cochlear fluids) and then to take 37.5 mg qid orally for the remainder of the week. None of the six patients reported a reduction in tinnitus on this modified regimen. Thus, the hypothesis that "therapeutic window" concentrations increase to "side effect" concentrations with constant dosage remains unsubstantiated.

Several of the patients[3] reported a worsening of their tinnitus in the week following AOAA administration. It may have been that AOAA reduced the tinnitus so gradually that improvement went unnoticed. On withdrawal from AOAA therapy, the patients reported what they perceived to be a worsening of tinnitus.

One interesting suggestion concerning the progression of tinnitus is that it may originate peripherally but that the site of generation of the perception then becomes central, much as patients feel "phantom limb" pain after the offending limb is lost. Dickins[17] suggested that tinnitus may be similar to pain that appears after an injury is healed and may be due to the discharges of deafferented secondary neurons. The progression of site from that of the origin to a more central one also occurs in the phenomenon of "kindling" seen in experimental epilepsy.[18] House and Brackmann[19] suggested that while tinnitus may start clinically as a symptom of end organ disease, it may induce long-term changes in central activity, since sectioning of the eighth nerve often fails to change tinnitus at all. Tyler[20] pointed out that peripheral auditory disease typically results in a degeneration of auditory nerve fibers that alters the normal input to the cochlear nucleus. In more recent times this has been confirmed and extended by Webster.[21] In our own patients, a hoped-for correlation with lidocaine or AOAA positivity and duration of tinnitus did not appear. We can shed no light on this problem. Therapy aimed at a peripheral site (ie, the EP) may be unsuccessful because the site for the generation of tinnitus has moved from the periphery, the original site, to the central auditory pathway.

Attempts at matching of tinnitus frequencies and intensities by the traditional method uncovered no consistent changes induced by the drug. However, well into the study attempts were made to match tinnitus intensity by the Goodwin and Johnson procedure.[22] This procedure seemed much more sensitive and reliably responsive to drug effects and correlated satisfactorily with the patient's subjective rating. However, complete data for the Goodwin and Johnson procedure were not available on a sufficient number of subjects to be included with this report.

Hearing aids, maskers, electrical stimulators, cochlear implants, surgical interventions, biofeedback, counselling, and drugs have been claimed useful in the amelioration of tinnitus. When the pharmacologist looks at such a long list of agents used to treat a disease or a symptom of a disease, the usual reaction is, "There must not be a magic bullet." If there were a magic bullet then the treatment list would be very short. Magic bullets generally act on the cause of the disease or symptom. In the case of tinnitus there are multiple causes and therefore no single "magic bullet" may ever emerge.

Another approach to controlling a symptom such as tinnitus that has many causes is to aim downstream of the cause at the common pathway over which the symptom is conducted. By interdicting the symptom at such a downstream site, causation becomes less important a factor in determining choice of therapy, but the therapy becomes symptomatically directed instead of causally directed. Specificity of drug action (ie, designing or selecting a drug with actions only or especially in the auditory pathway) may be had by aiming drugs at processes unique to the auditory pathway. Such unique processes lie primarily in the inner ear and not in the central auditory pathway. In its physiology the central auditory pathway is like many other hierarchical central pathways. Because of this similarity in physiology, drugs aimed at the central auditory pathway likely may affect nonauditory structures and thus cause side effects. On the other hand, drugs aimed at some uniquely auditory process (eg, the EP) may gain specificity of action. If the process aimed at is upstream (ie, cochlear processes), then selectivity is gained at the expense of broadness or inclusiveness of action. Here is the central problem in the pharmacotherapy of tinnitus: if one aims a drug downstream (ie, at the central auditory pathway), then one loses specificity or gains side effects. This is the difficulty with using local anesthetics such as lidocaine or anticonvulsant drugs such as AOAA in the palliation of tinnitus.

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EPIDERMAL GROWTH FACTOR BINDING AND ACTION ON TYMPANIC MEMBRANES

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A significant percentage of tympanic membrane (TM) perforations require some form of therapy to heal. Topical application of epidermal growth factor (EGF), a potent mitogen for epidermal and mesodermal cells, promotes healing of injuries in tissues histologically similar to TM, such as cornea and skin. We evaluated TM as a target tissue for EGF action. Specific, high affinity receptors for EGF were detected in TM (Kd = 3.1 n*M*, 150 fmol receptor/mg protein). Autoradiography of iodine 125-EGF binding to intact TMs revealed that EGF receptors were present on cells in the stratified squamous epithelial layer and in the stromal/mucoepithelial layer. Repetitive treatment of perforated cat TMs with 20 μg of EGF formulated in saline induced substantial hyperplasia of epithelial and stromal layers compared to paired TMs treated with saline. A single treatment of perforated cat TMs with 50 μg of EGF formulated in a hydrogel or in shredded Gelfoam produced significantly ($p < .05$) smaller perforations at 6 days following the operation compared to paired TMs treated with vehicles. These results demonstrate that TM is a target tissue for EGF and that topical treatment with EGF stimulates healing of TM perforations.

KEY WORDS — epidermal growth factor, tympanic membrane, wound healing.

INTRODUCTION

Perforation of the tympanic membrane (TM) is a common consequence of infection or trauma, and although most perforations heal unassisted, a substantial percentage of TM perforations fail to heal spontaneously and eventually may require additional therapy including surgical intervention.[1] Very early attempts to stimulate healing of TM perforations involved cauterization by topical application of silver nitrate[2] or 10% trichloroacetic acid.[3] These agents proved unsatisfactory, primarily because of inconsistent results and the need for prolonged, repeated treatments. Recent approaches to promoting healing include early patching of perforations with paper tape,[4] and treatment of experimental myringotomies in rats with hyaluronic acid.[5] These methods utilize materials that either provide a surface that promotes migration of regenerating epithelial cells or remove epithelial overgrowth of wound margins.

Epidermal growth factor (EGF) is a potent mitogen for epidermal cells and stromal fibroblasts in culture.[6,7] Epidermal growth factor receptors have been detected in many epithelial and stromal tissues, some of which share structural similarities with TM.[8,9] Topical treatment of injuries with EGF accelerates healing in tissues such as cornea and skin.[10-12] To determine if TM is a target tissue for EGF, we biochemically characterized binding of iodine 125-EGF to intact porcine TMs and localized EGF receptors in TM layers using autoradiography. We also evaluated the effect of topical EGF treatment on healing of perforated cat TMs.

MATERIALS AND METHODS

Chromatographically pure EGF was provided by Dr Carlos Nascimento of Chiron Corporation, Emeryville, Calif, and was synthesized by yeast cells transfected with a plasmid containing a synthetic gene coding for human EGF.[13] The EGF was iodinated by use of chloramine-T to a specific activity of 200 μCi/μg.[7]

Autoradiography of EGF Binding to TM. Three pairs of intact porcine TMs were obtained immediately after death by use of a microsurgical technique via a middle cranial fossa approach. The TMs were incubated for 2 hours at 37°C in chemically defined medium (CDM; equal parts of Medium 199, Ham's F-10, and Dulbecco's modified Eagle's medium buffered with 25 mM HEPES, and containing antibiotic-antimycotic agents [GIBCO]) containing 1 n*M* ^{125}I-EGF with or without 100 n*M* unlabeled EGF to detect nonspecific binding and total binding, respectively. Following incubation, TMs were washed in CDM, fixed in 10% neutral buffered formalin, and embedded in JB-4 resin (Poly-

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From the Department of Surgery, Division of Otolaryngology (O'Daniel, Petitjean, Jones, Martinez, Nolph), and the Department of Biochemistry (Zogg, Schultz), University of Louisville, Louisville, Kentucky. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Louisville.

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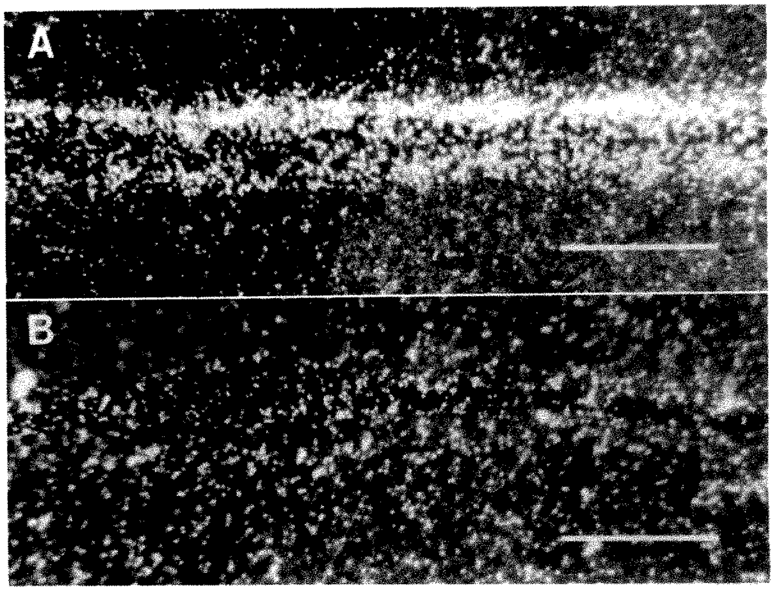

Fig 1. Autoradiography of iodine 125-epidermal growth factor binding to tympanic membranes. Photographs shown are representative of central region of tympanic membranes with stratified squamous epithelium oriented to top and viewed with dark-field illumination. Bars — 400 μm. A) Total binding. B) Nonspecific binding of iodine 125-epidermal growth factor.

sciences, Inc). Ten-micron-thick sections were coated with photographic emulsion (NTB-2, Kodak) and developed with Dektol after 10 days of exposure at 4°C. Analysis of grain density was performed on representative enlarged photographs of total and nonspecific binding specimens by counting eight randomly selected sites (1 cm^2) that overlay either the stratified squamous epithelial layer or the combined stromal and mucosal epithelial layers. Grain counts representing specific binding to epithelial layer or stromal/mucoepithelial cell layer were calculated by subtracting the average nonspecific grain counts for each cell layer from the average total grain counts for each cell layer. Grain densities attributed to specific binding were compared for statistical significance by use of Student's t test. Resolution values for radiation spread from ^{125}I in autoradiography have been reported previously,[14] and half distance values are sufficiently small (less than 4 μm) to allow assignment of grains to the cell layers.

Biochemical Characterization of EGF Binding to TM. Intact TMs obtained as described above were incubated in triplicate in CDM containing ^{125}I-EGF (100 p*M*) with increasing levels of unlabeled EGF from 10 p*M* to 1 μM for 2 hours at 37°C. The TMs were washed and radioactivity was measured with a Beckman 4000 BioGamma scintillation counter. Specific binding was calculated and transformed by the method of Scatchard.[15] Equilibrium dissociation constant and number of EGF binding sites were calculated from the line obtained by the least squares method of linear regression. The EGF binding was expressed as femtomoles EGF bound specifically per milligram of protein as measured by a dye binding assay (BCA, Pierce Chemical Co).

Specificity of ^{125}I-EGF binding to TMs was evaluated by use of a similar technique. Intact TMs were incubated in triplicate in CDM containing ^{125}I-EGF (100 p*M*, 50,000 counts per minute) with one of the following unlabeled proteins: nerve growth factor (10 n*M*), insulin (100 n*M*), angiotensin-II (100 n*M*), or EGF (100 n*M*). After 2 hours at 37°C, the TMs were washed in CMD and their radioactivity was measured in a gamma scintillation counter.

Effect of EGF on Healing of TM Perforations In Vivo. Meatoplasties were performed on sex- and age-randomized domestic cats under general endotracheal anesthesia with gentamicin given perioperatively. Meatoplasties were allowed to heal prior to TM perforation.

In the first experimental protocol, four cats underwent 50% TM perforations posterior to the malleus, and one ear of each cat was treated twice daily with 200 μL of phosphate-buffered saline (PBS) containing 20 μg of EGF while the opposite ear received 200 μL of PBS. Silicone ear plugs were

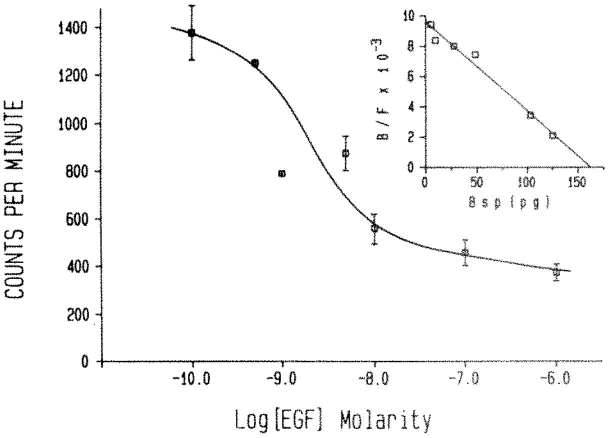

Fig 2. Characterization of epidermal growth factor (EGF) binding to tympanic membrane. Values plotted are mean and standard error. Specific binding was transformed by method of Scatchard[15] (inset). B/F — bound/free, Bsp — bound specifically.

TABLE 1. SPECIFICITY OF EPIDERMAL GROWTH FACTOR BINDING TO TYMPANIC MEMBRANE

Hormone	*Counts per Minute* *Mean ± Range*	*Percent Binding*
Iodine 125–epidermal growth factor	1,487 ± 438	100
Epidermal growth factor	499 ± 72	34
Nerve growth factor	1,397 ± 444	94
Angiotensin-II	1,250 ± 269	84
Insulin	1,309 ± 662	88

placed in the external auditory canal after each treatment. Treatment was continued until both perforations appeared closed by visual examination with an operating microscope. Following euthanasia, TMs were fixed in situ with 10% formalin and removed along with the annulus, then embedded in paraffin. Cross sections were cut through the original perforation site, stained with hematoxylin and eosin, and evaluated by light microscopy.

In the second experimental protocol, four cats underwent bilateral, total TM perforations. In three cats, the middle ear and proximal external auditory canal of one ear were filled with 500 μL of a hydrogel containing 125 μg of EGF, and the other ear received 500 μL of hydrogel alone. In one cat, the middle ear and external auditory canal of one ear were packed with 500 μL of shredded Gelfoam sponge (Upjohn) hydrated with saline containing 50 μg of EGF, while the opposite ear was packed with Gelfoam hydrated with saline. Silicone ear plugs were inserted, and the pinnae were sewn over the plugs. The presence of hydrogel or Gelfoam in the external canal prevented daily observations.

Six days following the operation, the cats were killed painlessly and TMs were fixed in situ with 10% formalin and removed with the annulus. The area of residual perforation and the area within the annulus for each TM were measured by computerized planimetry of enlarged photographs. The extent of healing in each TM was expressed as a percentage of the total area of the TM. The effect of EGF on healing of TMs was evaluated for statistical significance by use of a paired *t* test.

RESULTS

Autoradiography of EGF Binding to TM. Autoradiographic grain patterns demonstrated that all three cell layers of TMs specifically bound ^{125}I-EGF (Fig 1). Furthermore, the density of autoradiographic grains representing specific binding to the stratified squamous epithelial layer (36 grains/cm^2) was approximately twice as high as the density of specific grains over the combined stromal/mucoepithelial layers (17 grains/cm^2) ($p < .001$).

Biochemical Characterization of EGF Binding to TM. Competitive displacement of ^{125}I-EGF binding by unlabeled EGF to intact porcine TMs (Fig 2) generated a sigmoidal curve with increasing concentrations of unlabeled EGF. Transformation of specific EGF binding by the method of Scatchard[15] generated a linear plot with a correlation coefficient of 0.98, from which the equilibrium dissociation constant was calculated to be 3.1 n*M* and a maximum number of specific EGF binding sites was calculated to be 150 fmol/mg protein (Fig 2, inset).

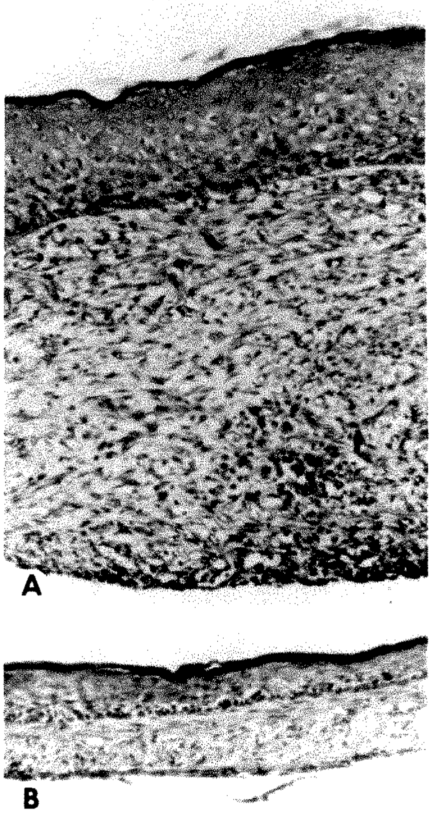

Fig 3. Histology of perforated cat tympanic membranes treated with A) epidermal growth factor in phosphate-buffered saline or B) vehicle alone (original x200).

As shown in Table 1, ^{125}I-EGF binding to intact porcine TMs was highly specific, as demonstrated by the inability of high concentrations of unlabeled insulin, nerve growth factor, and angiotensin-II to compete effectively for EGF binding.

Effect of EGF on Healing of TM Perforations In Vivo. In the first protocol, light microscopic examination of cross sections of the four pairs of TMs with partial perforations treated daily with PBS or PBS containing EGF showed that EGF treatment consistently induced substantially more hyperplasia of stromal and stratified epithelial layers as compared to paired TMs treated with PBS. Representative photomicrographs of TMs from a cat treated with EGF and PBS vehicle are shown in Fig 3.

In the second protocol, quantitative planimetry was used to determine the effect of a single application of EGF on healing of TMs 6 days after total perforations were made. As shown in Table 2, the

TABLE 2. EFFECT OF EPIDERMAL GROWTH FACTOR ON HEALING TYMPANIC MEMBRANE PERFORATIONS

		Percent Tympanic Membrane Area Healed	
Cat	*Vehicle*	*Epidermal Growth Factor*	*Vehicle Alone*
1	Hydrogel	93	86*
2	Hydrogel	97	88*
3	Hydrogel	96	81*
4	Gelfoam	93	81

*p<.025, paired *t* test.

amount of healing in TMs treated once with hydrogel containing EGF was significantly (p<.025) greater than in paired TMs treated once with hydrogel alone. Photographs of TMs from the cat treated with EGF in Gelfoam vehicle and Gelfoam alone demonstrated similar results (Fig 4).

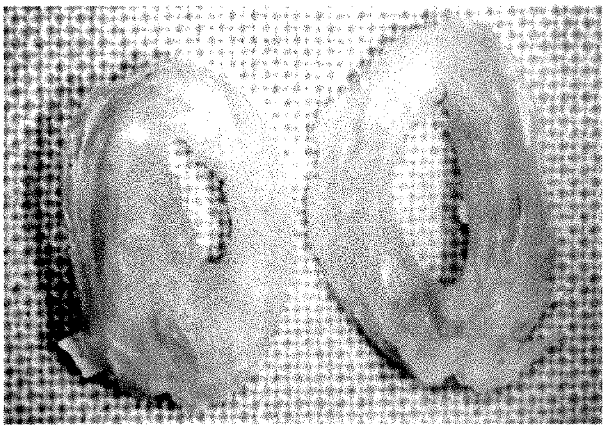

Fig 4. Gross morphology of perforated cat tympanic membranes treated with epidermal growth factor–impregnated Gelfoam (left) and saline-impregnated Gelfoam (right) (original x40).

DISCUSSION

Previous efforts to accelerate healing of TM perforations have focused primarily on providing an extracellular matrix that would encourage cellular migration. For example, standard surgical treatments of chronic TM perforations utilize materials such as paper tape or chemically fixed temporalis fascial graft that essentially bridge the edges of TM perforations.[1,4]

We have investigated a different concept, based on the use of a mitogenic peptide growth factor, to stimulate healing of TM perforations. Epidermal growth factor has been reported to stimulate healing of injuries in other tissues, such as skin and cornea, that are composed predominantly of fibroblasts and epithelial cells, as is the TM.[10-12] Our results demonstrate that TMs express specific, high affinity receptors for EGF. The affinity of the EGF receptor measured in TM (3 n*M*) is similar to the affinity of EGF receptors measured in other tissues, such as rat keratocytes (3 n*M*).[8] Also, the level of EGF receptors in TM (150 fmol/mg protein) is comparable to levels measured in normal cells and in human squamous cell carcinomas (10 to 450 fmol/mg protein).[16] Furthermore, autoradiography demonstrates EGF receptors to be present on all three histologic layers of the TM, with the greatest concentration in the stratified squamous epithelial layer. Thus, results of these in vitro biochemical studies suggest that TM is a potential target tissue for EGF action in vivo.

Results of the in vivo studies in cats demonstrate that EGF treatment influences healing of TM perforations. Daily application of EGF in PBS induced greater hyperplasia of epithelial and stromal cell layers than in controls. The hyperplastic response to EGF treatment in both cell layers is consistent with the detection of EGF receptors by autoradiography in both the epithelial and stromal/mucoepithelial cell layers.

It may be possible to improve the effects of EGF treatment by combining EGF with extracellular matrix components. For example, formulating EGF with hydrogel, Gelfoam, or collagen may provide both continuous mitogenic stimulation and a scaffolding structure to direct the pattern of regenerating tissue. The importance of prolonged exposure of cells to EGF was demonstrated both in vitro and in vivo, where cultured cells required 6 to 12 hours of continuous exposure to EGF to stimulate mitosis,[7,17] and mid-dermal burns required EGF formulated in a cream to stimulate healing.[10]

Currently, there is a need for a topical agent that will accelerate healing of persistent TM perforations without surgery. Our results demonstrate that EGF can influence healing of TM perforations in cats. Thus, the use of growth factors in combination with other materials may be a useful adjuvant in the management of persistent TM perforations.

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IMAGING CASE STUDY OF THE MONTH

MULTIPLE PARAGANGLIOMAS

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Paragangliomas (chromaffin body tumors) of the head and neck are tumors of tissue derived from the neural crest and are believed to function as chemosensory reflex receptors that respond to changes in their chemical environment.[1] The incidence of multiple paragangliomas is well documented. About 3% of all patients with this tumor and 26% of patients with a family tendency for the disease have multiple tumors.[2]

CASE REPORT

A 34-year-old woman presented with a neck mass on the right side that had grown progressively over the previous 5 months. She denied other symptoms such as neck pain, dysphagia, hoarseness, nasal obstruction, and epistaxis. The patient is a nonsmoker. Her right neck mass, extending from the retromandibular area to the midanterior sternocleidomastoid muscle, was mobile anteroposteriorly but not vertically. No bruit was felt over the mass.

Magnetic resonance studies were used to evaluate the right neck mass. The coronal T1 MRI view in the Figure, A, represents a section through the plane of the axis vertebra. This shows the large right-sided mass beginning at the level of the carotid artery bifurcation and extending upward to the level of the atlas vertebra. A second, smaller mass was present in the carotid bifurcation on the left side. Another, higher mass was also present on the left. The lesions on both sides were characterized by low signal intensity compared to that of fat, but a greater signal than that of muscle. Black areas of flow void were scattered through the lesions on both sides. Prominent medial displacement of the right jugular vein was present.

Axial T2-weighted studies also were obtained. The Figure, B, is a view just above the carotid artery bifurcation. Bright signal intensity due to the water content is present in both lesions. Faint areas of flow void are also present. Carotid artery branch separation is marked on the right. Lesser separation is present on the left.

A higher axial T2-weighted MRI study is shown in the Figure, C. The section is at the level of the anterior arch of the atlas. The bright signal of the high lesion on the left is seen just behind the carotid artery as it enters the temporal bone. A flow void produces the small area of decreased signal in the anterior portion of the lesion at this location.

Surgical resection of the suspected right carotid body tumor revealed a combined carotid body and glomus vagale tumor. A carotid body tumor and glomus jugulare tumor were removed from the left side during a later surgical procedure.

DISCUSSION

Head and neck paragangliomas may occur in the carotid body, on the vagus nerve, along the jugular vein, in the middle ear over the cochlear promontory, in the orbit, and in the larynx. The neck masses begin as slow-growing, initially painless masses that may become painful as they enlarge.

The preliminary workup for a suspected neoplasm of the carotid body commonly consists of a computed tomographic scan and a bilateral carotid arteriogram. Paragangliomas are vascular and have a diffuse, opaque appearance resembling a blush on angiography. Carotid body paragangliomas consistently show a blush appearance at the carotid bifurcation, with displacement of the internal and external carotid arteries. Although reported experience with MRI is limited, Olsen et al[3] published findings on 15 paragangliomas in ten patients. They concluded that tumors larger than 2 cm showed a

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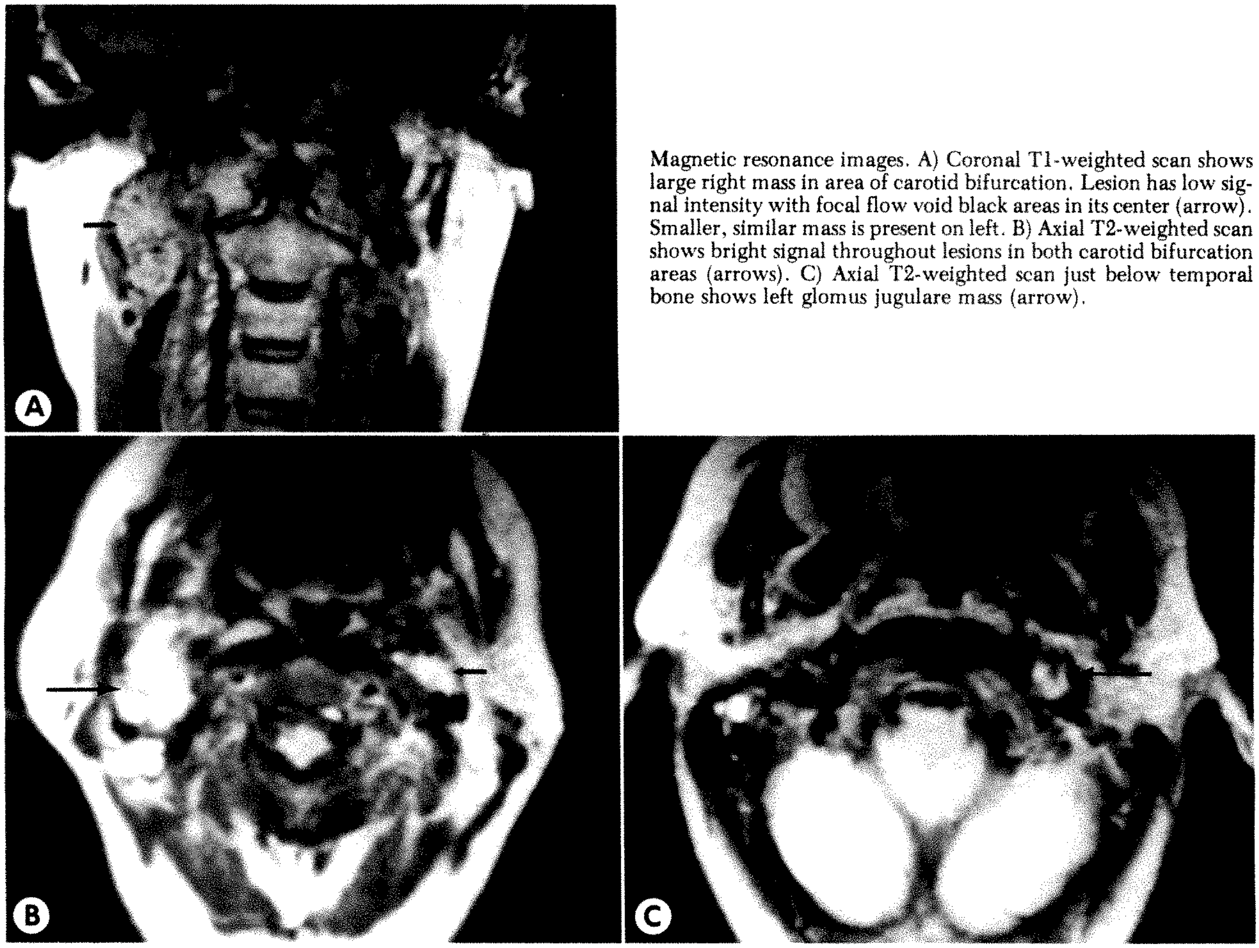

Magnetic resonance images. A) Coronal T1-weighted scan shows large right mass in area of carotid bifurcation. Lesion has low signal intensity with focal flow void black areas in its center (arrow). Smaller, similar mass is present on left. B) Axial T2-weighted scan shows bright signal throughout lesions in both carotid bifurcation areas (arrows). C) Axial T2-weighted scan just below temporal bone shows left glomus jugulare mass (arrow).

characteristic salt-and-pepper pattern caused by high vascular flow areas interspersed among slowly flowing blood and tumor cells. To the extent that this pattern is generally characteristic of paragangliomas, MRI would be a useful diagnostic tool. We are suggesting MRI as an adjunct to CT, which is superior in demonstrating subtle osseous changes in relation to the skull base.

The role of MRI in evaluation is greatest in the early stages of the tumor. Although arteriography may be superior in the evaluation of vessels in preoperative planning, MRI also may be useful in providing anatomic localization and defining relationships to major surrounding vascular structures, which is necessary for planning radiation therapy.[3] Upon retrospective review of our patient, the right paragangliomas show a fissure (see Figure, A). This probably represents a separation between the vagale and the carotid body tumor.

When tumors of the carotid body and/or other paragangliomas are suspected, careful bilateral evaluation of the carotid bifurcation is indicated. Arteriography documents the condition of blood-supplying vessels and is useful in identifying small paragangliomas. Magnetic resonance study shows the integrity of normal vascular structures and may demonstrate changes in blood flow due to the tumor mass. It is superior to CT in these respects and therefore might be considered prior to CT in diagnosing cases of suspected paragangliomas. Magnetic resonance is not as effective as CT, however, in demonstrating osseous changes.

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PATHOLOGY CONSULTATION

SQUAMOUS CARCINOMAS WITH GLANDLIKE (ADENOID) FEATURES

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Squamous cell carcinomas with a prominent glandlike histologic component are uncommon histologic variants found in the skin and mucous membranes. Although not restricted to the head and neck, they have a predilection for that anatomic area. Lost in the debate over their histogenesis are repeated observations that the carcinomas have an aggressiveness and life-consuming capacity that exceed those of conventional squamous cell carcinomas.

Phenotypic expressions of squamous cell carcinoma range from the differentiated verrucous carcinoma to lesions distinguishable as squamous in lineage only after special studies. There are mucosal and cutaneous counterparts in nearly every instance. The scenario that follows first recognition of the squamous cell variants is fairly predictable: sporadic reporting of additional cases and, in the event, an acquisition of descriptive synonyms, followed by debate over histogenesis and finally nosologic acceptance. Often lost in the sequence is clinicopathologic correlation.

Squamous cell carcinomas of the skin and mucous membranes that display a glandlike pattern in a variable degree are typical of the genre. Over the past 40 years, these carcinomas have been called adenoid squamous, adenosquamous, acantholytic squamous, pseudoglandular squamous carcinomas, and even adenocanthoma.[1-6] A consistent misdiagnosis has been mucoepidermoid carcinoma.[5,7,8] Demonstrable malignant behavior has eliminated adenocanthoma as a diagnosis.

The debate over histogenesis has centered on whether the eccrine ducts in the skin and excretory salivary ducts in the mucosa or whether basilar cells of the epidermis/mucosa are progenitors. The presence or absence of intracellular mucin, the diagnostic power of which is lamentably weak, is often used as the pivotal feature.[1]

Of far more importance is the prognostic significance of a diagnosis of these variants of squamous cell carcinoma. Since most of the carcinomas occur in the skin and mucous membranes of the head and neck, this is especially pertinent to the head and neck surgeon.

Although any of the synonyms except adenocanthoma can be used, we will, for purposes of this discussion, consider the lesions as adenoid squamous cell carcinomas. Adenoid squamous cell carcinoma is preponderantly a neoplasm of the skin and especially of the sun-exposed areas of the head and neck. Irrefutable examples have also been reported from mucosal sites. These include the vermilion borders of the lips, tongue, oral mucosa, nasopharynx, and larynx.[1-6] The present authors have also found the carcinoma in the sinonasal tract.

Adenoid, pseudoglandular features usually dominate the histologic appearance. These are usually found deep in the lesions or deceptively free of the overlying epidermis/mucosa beneath their surfaces (see Figure, A). The conventional squamous carcinoma component is nearly always well differentiated (see Figure, B). In some cases, the squamous elements may appear to be only hyperplastic. In the majority of the carcinomas the adenoid feature is initiated in the basal layer of the squamous epithelium (see Figure, C). Here it is manifested by a suprabasal clefting and acantholysis followed by a downward rather than upward progression. The end result is a seemingly biphasic carcinoma (see Figure, D). A third cytomorphologic component may also be seen. This one is much less differentiated and can be sarcomatoid, spindled, or clear cell in appearance. A desmoplastic reaction may be an accessory finding.

The important differential diagnosis is mucoepidermoid carcinoma, a lesion whose rather specific histologic criteria are too often stretched to include the adenoid squamous cell carcinoma.[7,8] The "epidermoid" in mucoepidermoid carcinoma is adjectival and precise. Rarely does a mucoepidermoid carcinoma have recognizable squamous features. It almost never keratinizes, and mucous cells are usually readily identified and not elusive.

It is our experience that a *mucosal* head and neck squamous cell carcinoma that demonstrates prominent adenoid features is a carcinoma that has a

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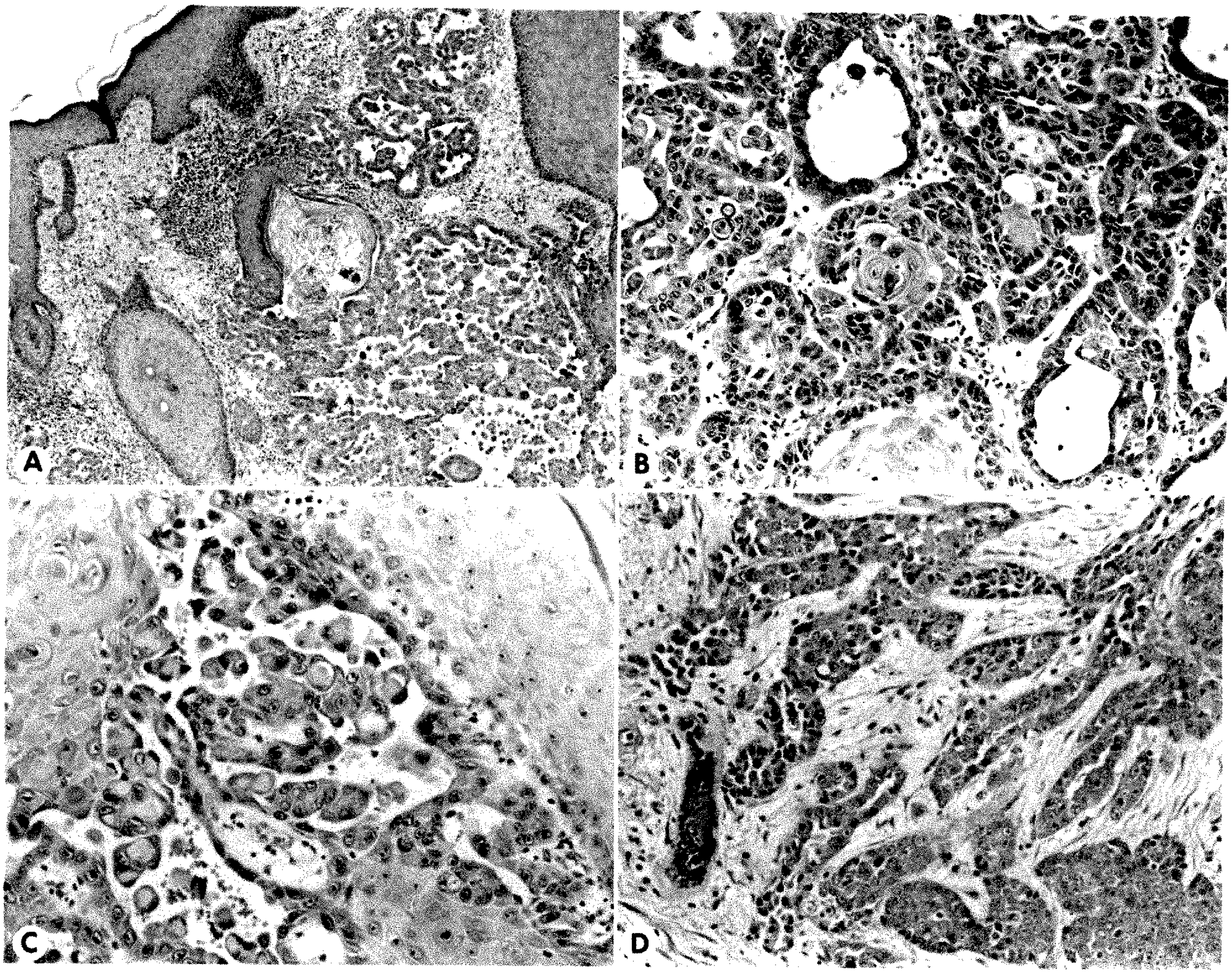

Adenoid squamous carcinoma. A) Of preauricular skin (H & E, original x40). Pseudoglandular carcinoma infiltrates beneath and adjacent to epidermis. B) Of skin, manifesting keratinizing and pseudoductal characteristics (H & E, original x120). C) Formative stage, showing acantholytic cleavage of basilar cells (H & E, original x200). D) Of hypopharynx (H & E, original x60). Invasive carcinoma manifests pseudoductal pattern as result of acantholytic clefts.

worse prognosis than conventional squamous cell carcinomas. This is clearly seen for basaloid-squamous carcinomas[9] and in the carcinomas reported by Zaatari and Santoianni,[4] Goldman et al,[6] Ferlito,[5] Damiani et al,[8] and Gerughty et al.[2] Less clear is the prognostic impact of adenoid features in cutaneous squamous cell carcinomas.[1,10] The differences in opinion may be unrelated to histologic appearances, with depth of invasion and clinical stage the determinant factors.

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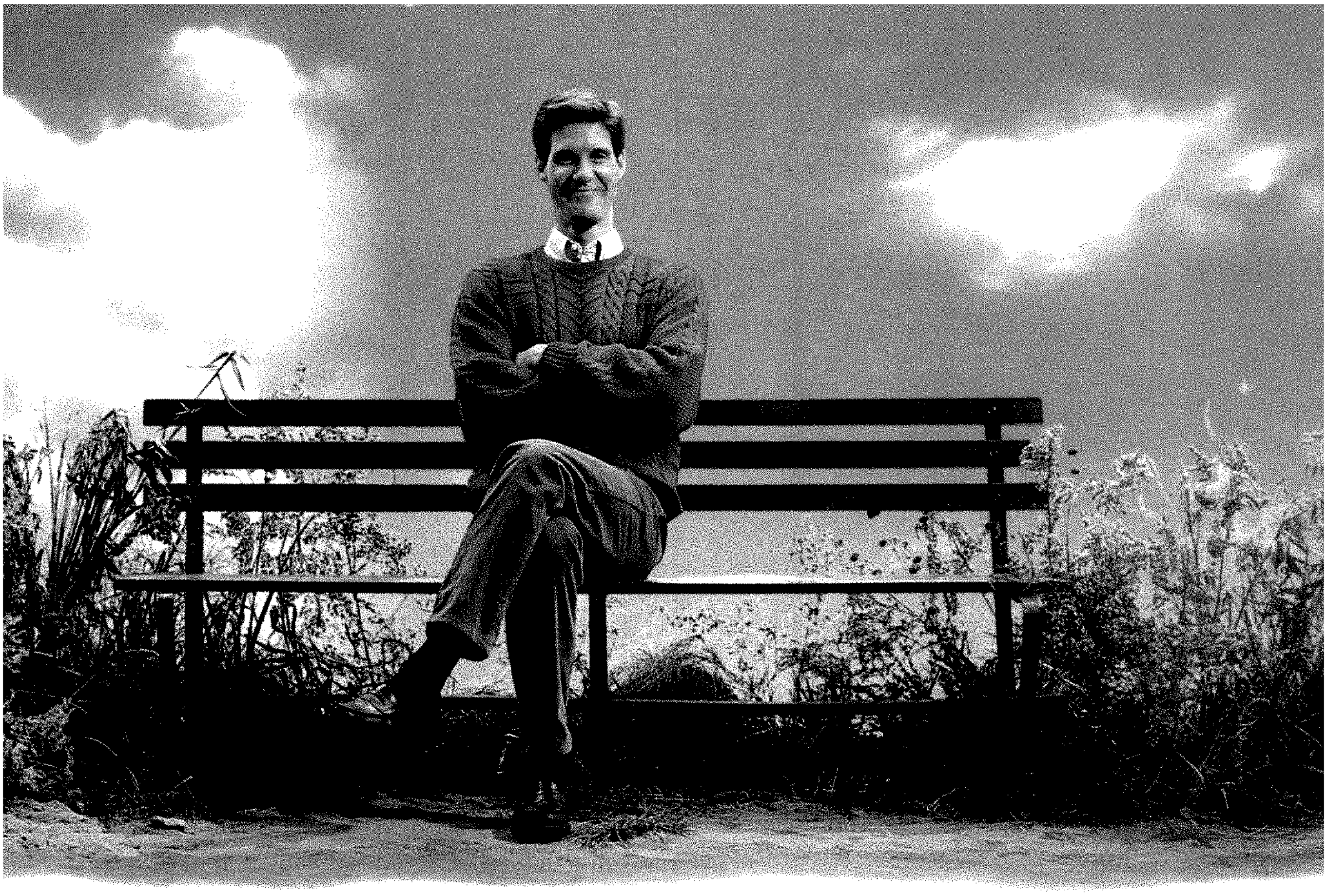

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*In two out of four measures of nasal symptoms, $P<0.01$.
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Beconase® Inhalation Aerosol
(beclomethasone dipropionate, USP)
For Nasal Inhalation Only

BRIEF SUMMARY

Beconase AQ® Nasal Spray, 0.042%*
(beclomethasone dipropionate, monohydrate)
***Calculated on the dried basis. For Intranasal Use Only.**

SHAKE WELL BEFORE USE.

The following is a brief summary only. Before prescribing, see complete prescribing information in Beconase® Inhalation Aerosol and Beconase AQ® Nasal Spray product labeling.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of either preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with Beconase® Inhalation Aerosol or Beconase AQ® Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to Beconase Inhalation Aerosol or Beconase AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with Beconase AQ® Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with Beconase® Inhalation Aerosol or Beconase AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping Beconase AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of Beconase Inhalation Aerosol or Beconase AQ Nasal Spray may suppress HPA function.

Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For either preparation to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with these preparations should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of these preparations into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using Beconase Inhalation Aerosol or Beconase AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses of Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be avoided.

Information for Patients: Patients being treated with Beconase Inhalation Aerosol or Beconase AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use these preparations at regular intervals since their effectiveness depends on their regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Beconase Inhalation Aerosol or Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of either unit and to attain maximum improvement, the patient should read and follow carefully the patient's instructions section of the package insert.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

Beconase® Inhalation Aerosol: Adverse reactions reported in controlled clinical trials and long-term open studies are described below. Sensations of irritation and burning in the nose (11 per 100 patients) following the use of Beconase Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

Beconase AQ® Nasal Spray: Adverse reactions reported in controlled clinical trials and open studies are described below.

Mild nasopharyngeal irritation has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.
RB2-1006 March 1989

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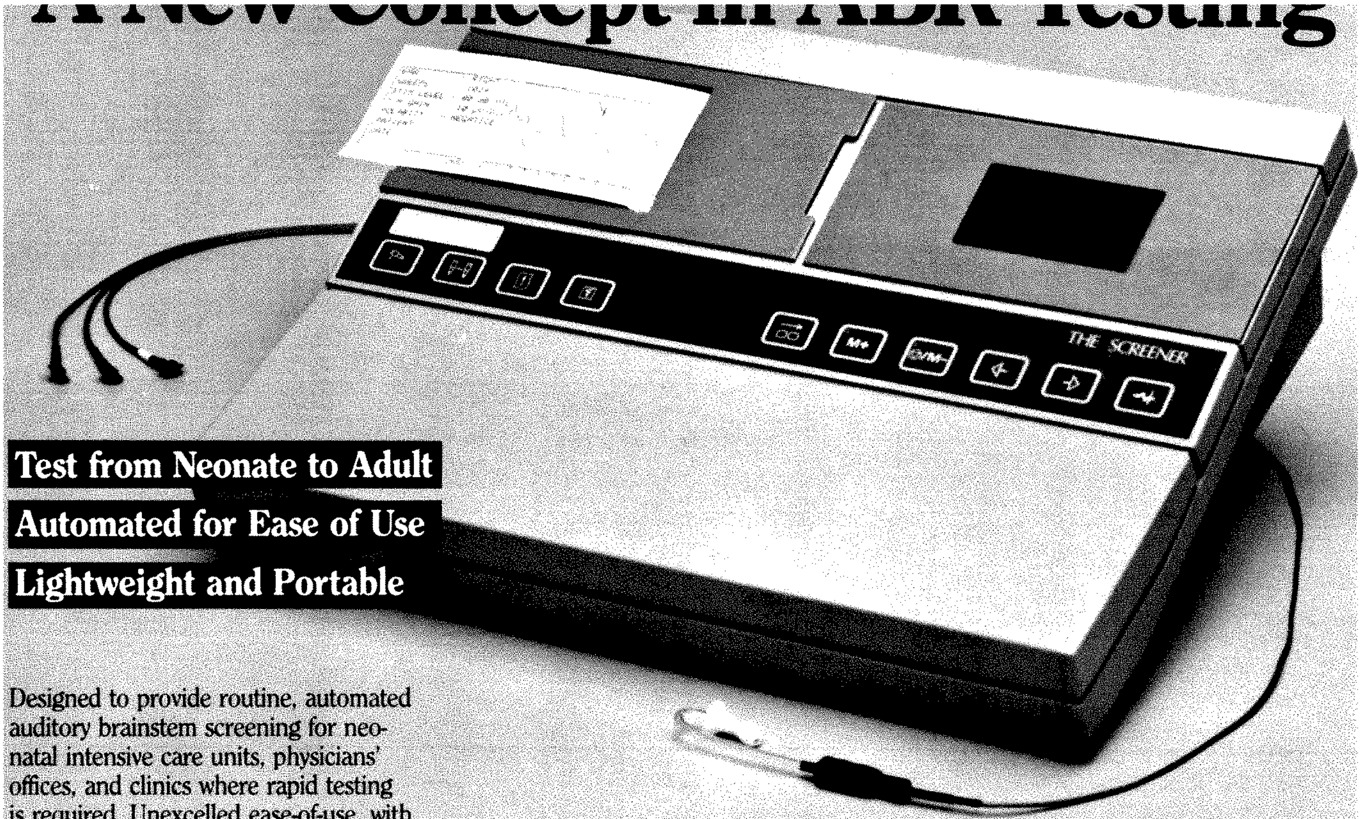

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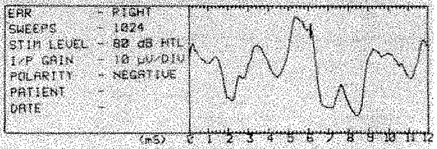

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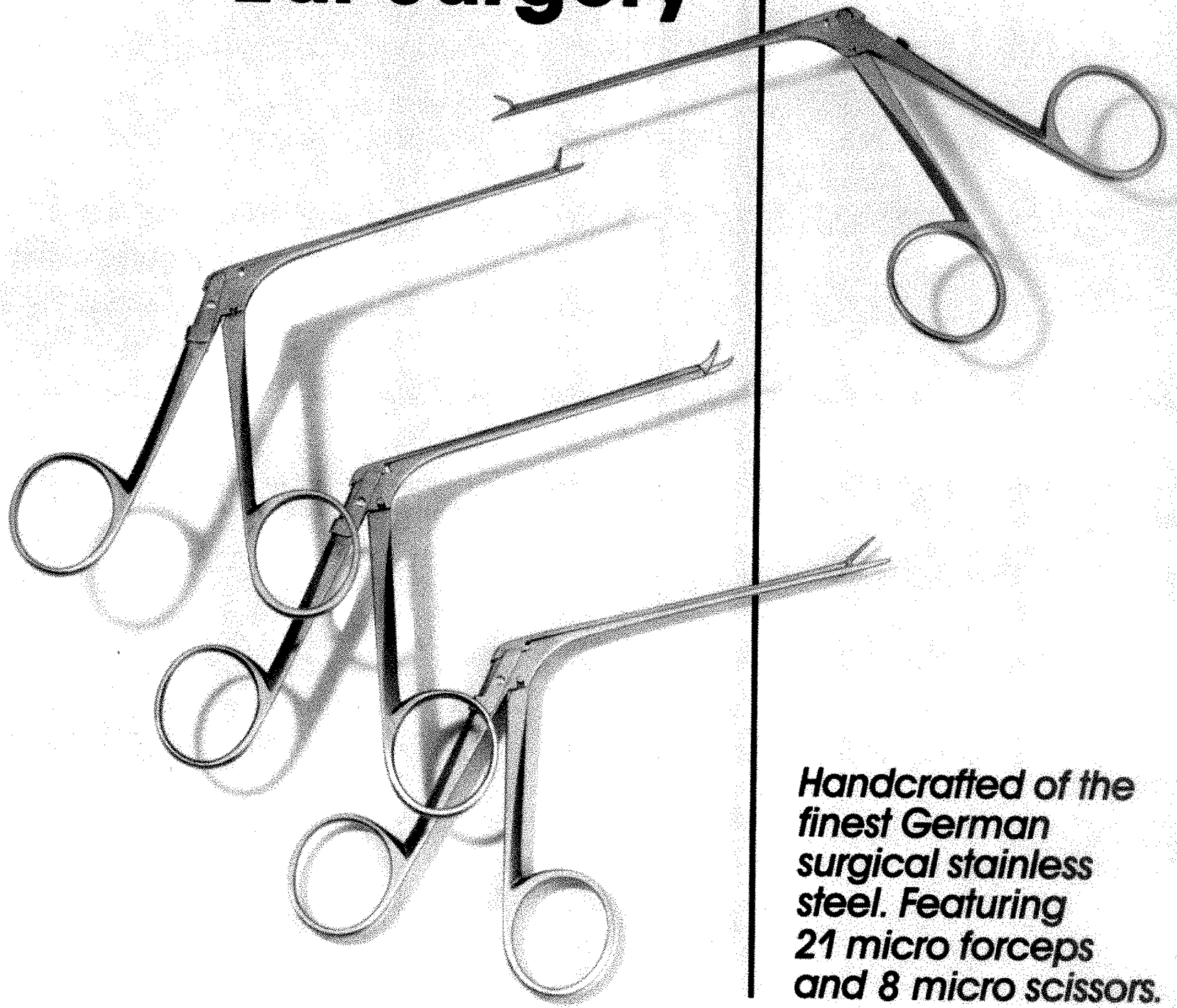

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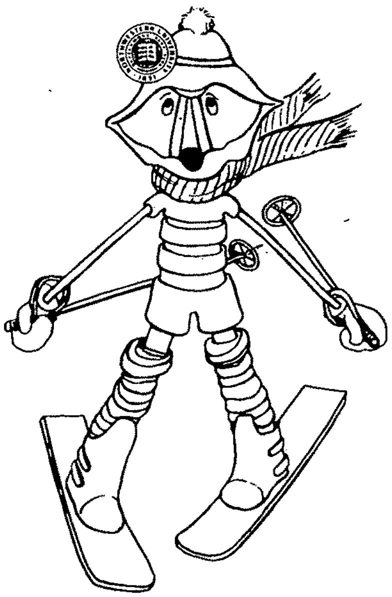

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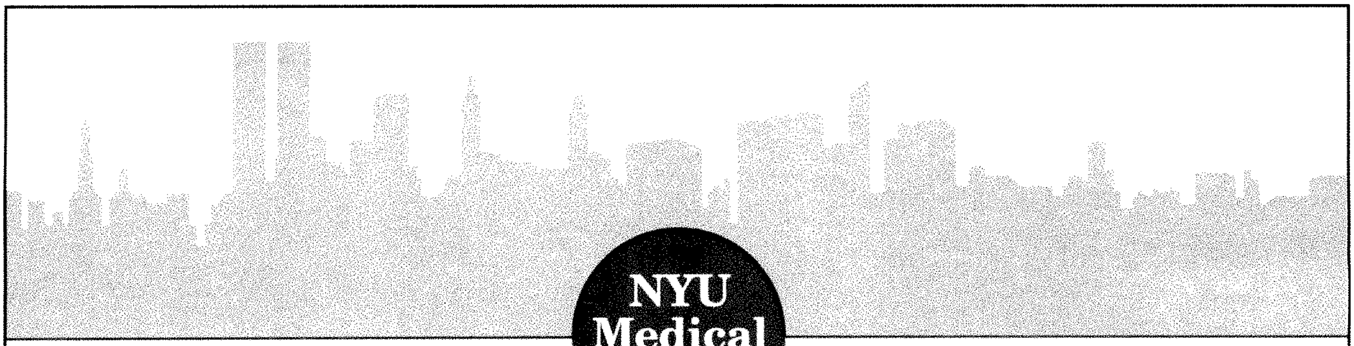

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BRONCHOGENIC CYST WITH TRACHEAL INVOLVEMENT

HOWARD M. YERMAN, MD LAUREN D. HOLINGER, MD

CHICAGO, ILLINOIS

Bronchogenic cysts are uncommon developmental anomalies of the primitive foregut that can produce symptoms of ventilatory compromise in infants and children. A 2-month-old child presented with episodes of stridor and obstructive apnea due to a bronchogenic cyst compressing the trachea and causing near-total obstruction. Aspiration of the cyst during bronchoscopy resulted in severe bradycardia (from 140 to 50 beats per minute), although blood pressure was stable and oxygen saturation remained at 100%. Subsequent elective thoracotomy revealed the cyst to be intimately associated with the vagus nerve, and vagal stimulation may have caused the bradycardia. Bronchogenic cysts, although rare, should be considered in the differential diagnosis of infants and children undergoing direct laryngoscopy and bronchoscopy for airway compromise. The endoscopic aspiration of cystic tracheal and bronchial lesions may not obviate the need for more definitive surgical treatment and, as this case demonstrates, is not free of potential hazard.

KEY WORDS — airway obstruction, bronchogenic cyst, foregut malformations, stridor.

INTRODUCTION

Infants and children with stridor are frequently referred to pediatric otolaryngologists for diagnosis and treatment. Common sources of stridor in the pediatric age group include laryngomalacia and tracheomalacia, subglottic stenosis, bilateral vocal cord paralysis, and vascular anomalies.[1] Bronchogenic cysts are an uncommon source of stridor in this population. Although they have been reported in infants and children since the late 17th century, only recently has attention been focused on the antemortem identification and successful treatment of these cysts in this age group.[2-7] Furthermore, despite the fact that these patient's symptoms often necessitate endoscopic evaluation, few reports appear in the otolaryngology literature.[8-12] We evaluated and treated a 2-month-old child with episodic stridor, apnea, and cyanosis due to a bronchogenic cyst. We describe this case and review the embryology, diagnostic evaluation, and management of this anomaly. Consideration of this entity in the differential diagnosis of stridor in the pediatric age group is emphasized, as are the potential complications of endoscopic manipulation of paratracheal masses.

CASE REPORT

A 2-month-old child was referred to the Children's Memorial Hospital of Chicago for evaluation of episodic stridor, with a single episode of obstructive apnea and cyanosis. The infant was the full-term product of an uncomplicated pregnancy and delivery. Her medical history prior to admission was unremarkable with the exception of the respiratory symptoms. Mild inspiratory stridor had been noted at birth. The stridor was not progressive and was unrelated to feedings or positioning. There was no history of intubation, fever, or upper respiratory tract infection. Evaluation prior to transfer included a normal chest radiograph, lateral neck xeroradiogram, and barium swallow (Fig 1). Physical examination at the time of admission revealed an apparently healthy child without respiratory distress. Mild inspiratory stridor was present with crying. No retractions were seen, and no cutaneous vascular lesions were identified. The remainder of the physical examination findings were normal.

Direct laryngoscopy and bronchoscopy were per-

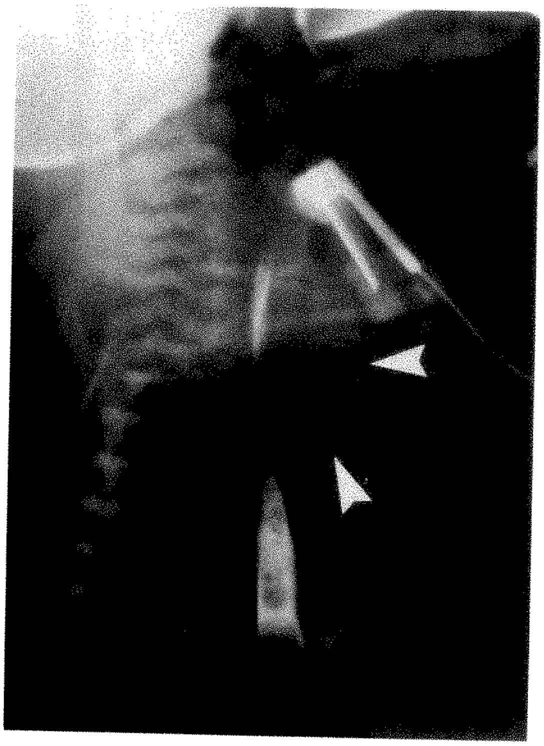

Fig 1. Barium swallow, reported as normal. In retrospect, ovoid soft tissue mass is identified anterior to esophageal barium column (arrowheads).

From the Department of Otolaryngology–Head & Neck Surgery, University of Illinois College of Medicine at Chicago (Yerman), the Division of Pediatric Otolaryngology, Children's Memorial Hospital of Chicago (Holinger), and the Department of Otolaryngology–Head and Neck Surgery, Northwestern University College of Medicine (Holinger), Chicago, Illinois.

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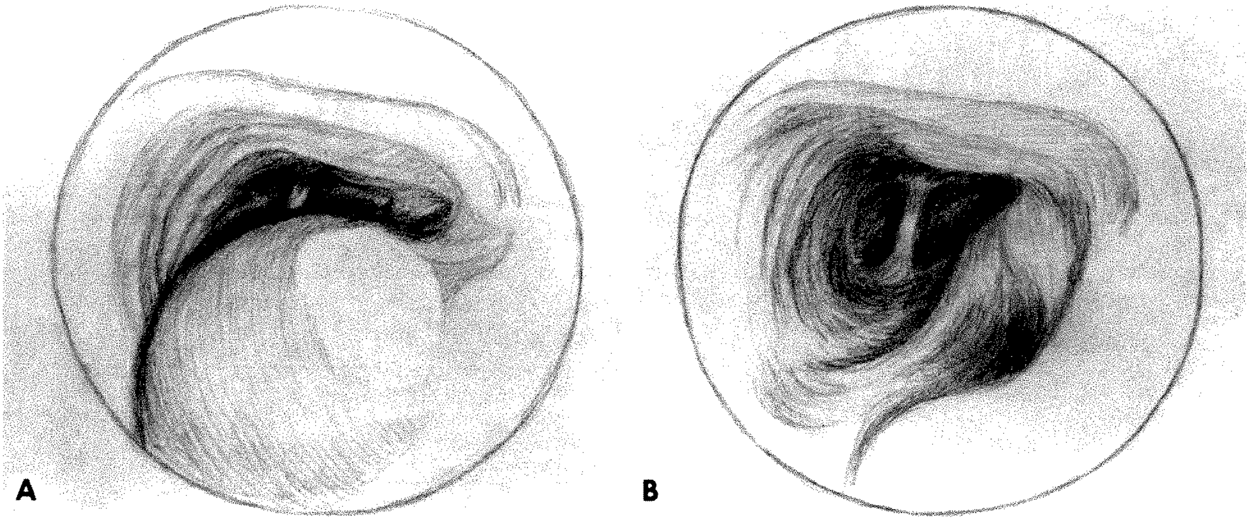

Fig 2. Diagrams of endoscopic view of tracheal lumen following aspiration of bronchogenic cyst. Note flaccidity of cyst wall with variation in ventilatory pressure, A) protruding into tracheal lumen and B) recessed into cyst cavity. Carina is seen in distance.

formed under general anesthesia supplemented with topical lidocaine hydrochloride spray. The larynx was normal. A translucent, nonpulsatile, cystic-appearing mass was identified at the midtracheal level. The mass had an intact mucosal cover and obstructed approximately 90% of the tracheal lumen. It was broadly based from the right lateral tracheal wall. The remainder of the tracheobronchial tree was normal.

The mass was decompressed with a sclerosing needle, and approximately 5 mL of a turbid, watery fluid was aspirated. The wall of the cyst collapsed immediately and fluctuated with positive pressure ventilation (Fig 2). Simultaneously, the patient developed severe bradycardia (from 140 to 50 beats per minute), although her blood pressure was stable and oxygen saturation remained at 100%. The bradycardia was unresponsive to a maximal dose of intravenous atropine sulfate (20 μg/kg), but ultimately responded to a single dose of intravenous epinephrine (10 μg/kg).

Chest radiography and computed tomography performed following bronchoscopy revealed an air-filled cyst adjacent to the trachea (Fig 3). Thoracotomy demonstrated the intimate association of the lesion to the vagus nerve (Fig 4), and we presume that vagal stimulation during cyst decompression was the cause of the bradycardia. Histopathologic examination of the lesion revealed features characteristic of a bronchogenic cyst (Fig 5). The patient's postoperative course was uneventful, and she remains symptom-free 15 months following treatment.

DISCUSSION

Bronchogenic cysts account for approximately 10% of all mediastinal masses in children.[13,14] Although over 100 cases had been reported in the world literature by 1908,[15] the first successful excision in a child did not occur until 1948.[3,5,6] Prior to this time, and for the ensuing decade, the diagnosis of a bronchogenic cyst in infants and children was most frequently made at autopsy.[16] More recently, death due to this congenital abnormality has been the exception, and successful surgical extirpation the rule.[7]

Embryologically, the lower respiratory system begins to develop at 4 weeks' gestational age. A median laryngotracheal groove forms from the caudal end of the ventral wall of the pharynx. As this diverticulum enlarges, tracheoesophageal folds develop bilaterally, and they eventually fuse to form the tracheoesophageal septum. This separates the developing respiratory tract from the esophagus. At the distal end of the laryngotracheal tube, two lung buds appear that eventually form mature lungs through repeated bifurcation and differentiation.[17] Bronchogenic cysts are thought to result from the abnormal budding of this primordial lung tissue.[3] Other developmental anomalies of the foregut, including pulmonary sequestrations and esophageal duplications, may occur by a similar mechanism.[18,19]

Bronchogenic cysts are most frequently unilocular and contain either clear fluid or, less commonly, hemorrhagic secretions or air. A patent connection with the airway is unusual. However, such a communication may be present and, when narrow, may promote cyst infection by allowing bacterial entry but not fluid egress. Histopathologic examination of the cyst wall demonstrates tissues normally found in the respiratory tract, including cartilage, smooth muscle, mucous glands, and fibrous connective tissue.[20] The epithelium is usually of a pseudostratified ciliated columnar type, unless prior infection has occurred, in which case a squamous epithelium may be found.[21]

While bronchogenic cysts are usually diagnosed

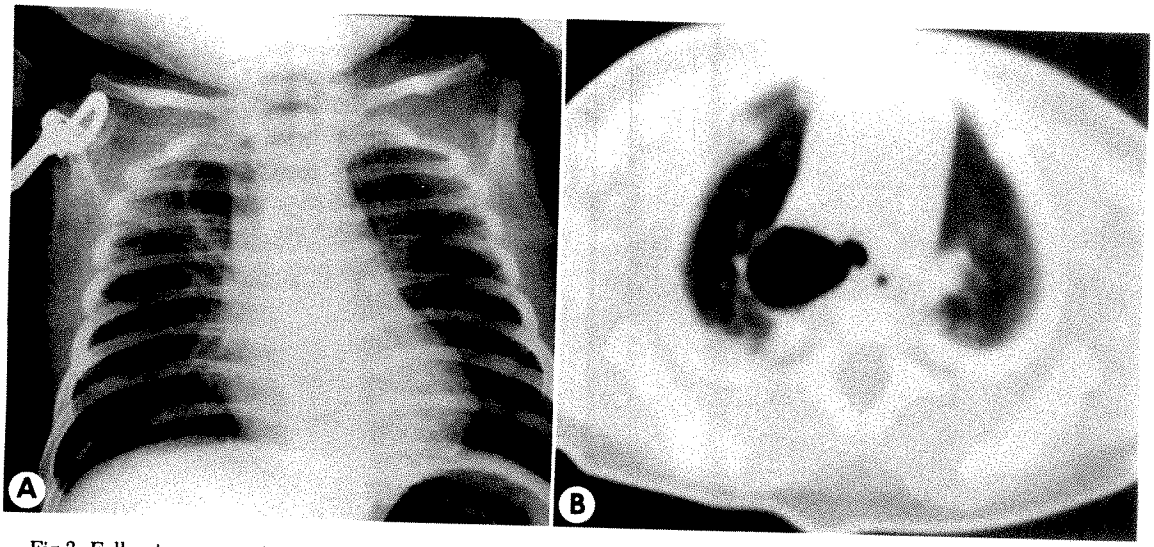

Fig 3. Following cyst aspiration, air-filled cyst is now recognizable in right upper lung field. A) Posteroanterior chest radiograph. B) Axial computed tomogram proximal to tracheal bifurcation.

in adults as incidental findings on chest radiographs obtained for other reasons, infants and children are more likely to be symptomatic. Symptoms are usually nonspecific and include many for which pediatric otolaryngology consultation is obtained. Snyder et al[7] describe 34 infants and children treated for bronchogenic cysts and esophageal duplications. Two thirds had symptoms that often require endoscopic evaluation, including persistent or recurrent pneumonia, airway obstruction manifested as stridor, cough or wheezing, and dysphagia. Evaluation often begins with chest and neck radiographs, as well as barium swallow study. This initial investigation is nondiagnostic in the majority of children with bronchogenic cysts.[7] Although some have suggested computed tomography as the next diagnostic study, endoscopy is a more appropriate next step. Direct laryngoscopy and bronchoscopy provide a diagnosis in the vast majority of infants and children with stridor. When endoscopy is not diagnostic or is suggestive of a mediastinal mass (extrinsic airway compression), then an axial imaging procedure of the chest may be beneficial.

There is general agreement that treatment of these lesions requires complete surgical extirpation. Recurrence following partial resection or needle aspiration has been described.[11,16] In these instances, recurrent symptoms occurred with fluid reaccumulation. There is a single report suggesting the possibility of complete cyst excision via an endoscopic approach.[8] The intratracheal location of the anomaly described in this report was indeed unique. We are unable to find other descriptions of attempted endoscopic management of bronchogenic cysts. Needle aspiration in our patient resulted in a bradycardia that was initially resistant to standard medical therapy. Since blood pressure and oxygenation remained stable, the bradycardia seems to have been a complication of vagal stimulation. Stimulation of the parasympathetic fibers of the vagus nerve reduces the rate of spontaneous depolarization of the sinoatrial node of the heart, thus resulting in a decreased heart rate. As there is no direct vagal influence on the vasculature, blood pressure is not affected. Vagus stimulation, either from pressure transmitted to the nerve as the needle enters the cyst or from decompression of the cyst with the

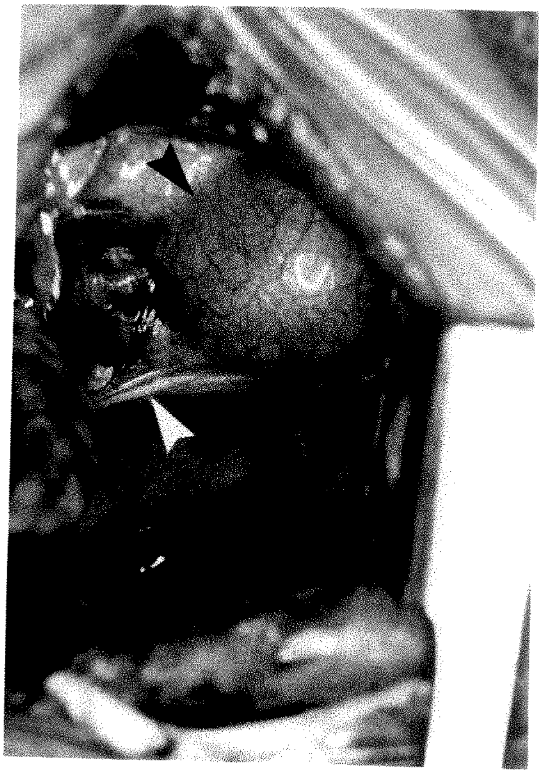

Fig 4. Intraoperative photograph of right tracheoesophageal groove and cyst (black arrowhead), showing relationship to vagus nerve (white arrowhead). Surgical approach is via right anterolateral thoracotomy; retractor is positioned on inferior edge of

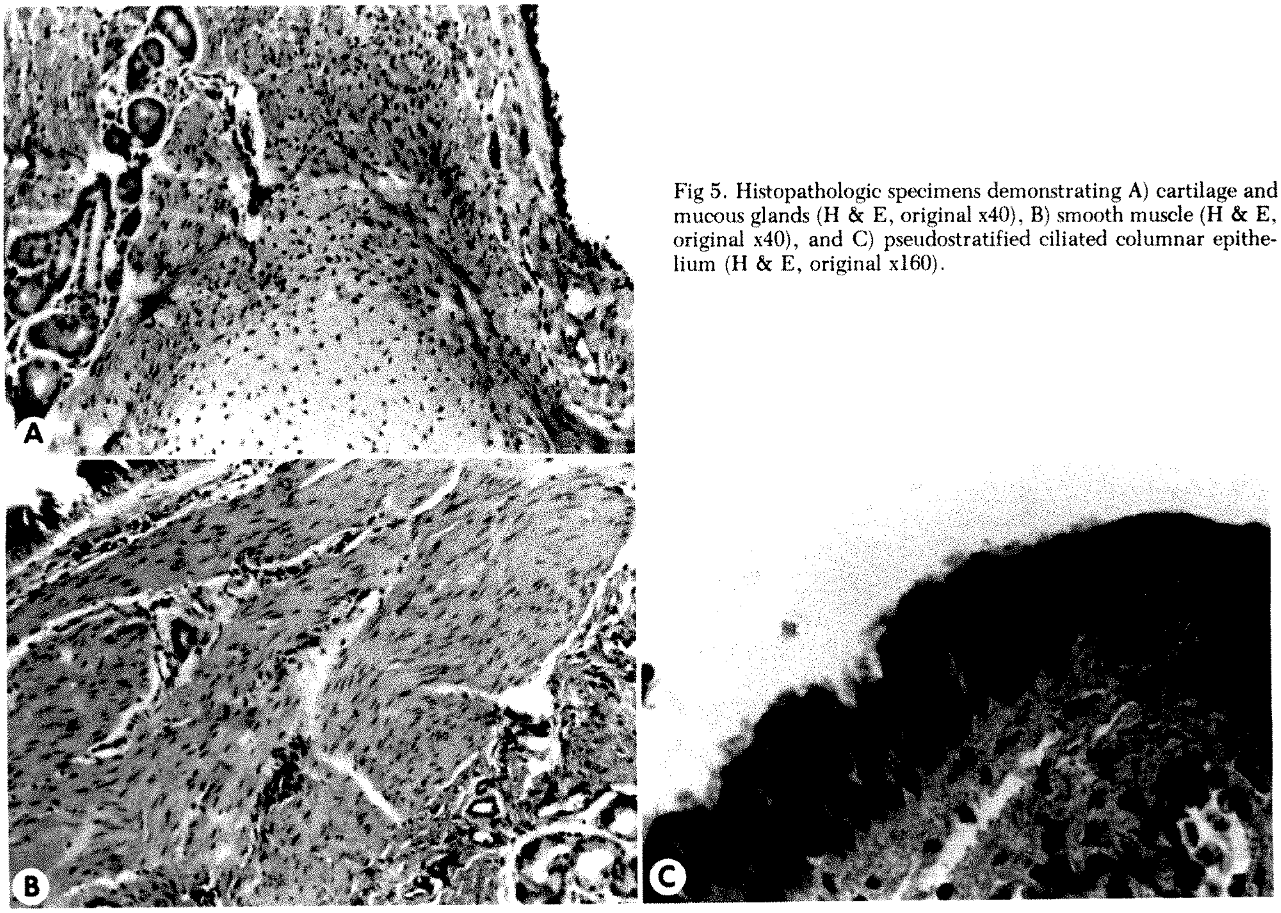

Fig 5. Histopathologic specimens demonstrating A) cartilage and mucous glands (H & E, original x40), B) smooth muscle (H & E, original x40), and C) pseudostratified ciliated columnar epithelium (H & E, original x160).

subsequent release of pressure from the nerve, would result in precisely the findings noted in our patient. The other potential source of bradycardia in our patient is too deep a plane of anesthesia; however, this is unlikely without both bradycardia and hypotension.

Needle aspiration is unlikely to bring about the definitive treatment of a mediastinal bronchogenic cyst. In addition to bradycardia, inadvertent penetration of a major vessel is another potential complication of needle aspiration of a paratracheal mass. Bronchoscopic control of brisk intratracheal hemorrhage may be difficult to achieve and may necessitate emergency thoracotomy. Despite the potential risks, needle aspiration may be warranted in selected cases, especially for patients with severe, symptomatic airway obstruction, for children whose conditions are too unstable for a major surgical procedure, and for children with infectious complications related to the cyst (cyst infection or obstructive pneumonia). In the majority of cases, prompt thoracotomy with complete surgical excision remains the treatment of choice for symptomatic mediastinal bronchogenic cysts. Tracheotomy has little role in treatment, as airway compression usually occurs proximal (toward the carina) to the tracheotomy site.[14]

CONCLUSION

Although uncommon, bronchogenic cysts are included in the differential diagnosis of airway obstruction in infants and children. Evaluation includes chest and neck radiographs as well as barium swallow study. When these procedures are nondiagnostic, direct laryngoscopy and bronchoscopy are undertaken as the next step in the diagnostic workup. When tracheal or bronchial compression from a previously unsuspected cystic mass is identified during bronchoscopy, manipulation must proceed with caution. If aspiration of a bronchogenic cyst is unlikely to offer significant clinical benefit, then the procedure should be avoided. The endoscopic aspiration of bronchogenic cysts is not without potential hazard, and thoracotomy with complete surgical excision is usually required to definitively treat these lesions.

ACKNOWLEDGMENT — We greatly appreciate the work of Karen Soprych in preparing the Fig 2 line drawings.

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SEVERE OTOLARYNGOLOGIC MANIFESTATIONS OF ARTHROGRYPOSIS MULTIPLEX CONGENITA

ALBERTO N. LAUREANO, MD   LEONARD P. RYBAK, MD, PHD
SPRINGFIELD, ILLINOIS

Arthrogryposis multiplex congenita (AMC) is a rare congenital disorder characterized by multiple fixed-joint deformities of the upper and lower extremities. Those afflicted with the more common neurogenic form of AMC can have otolaryngologic manifestations. Here, a case of AMC with severe otolaryngologic manifestations is reported. The clinically relevant findings included an expressionless face, micrognathia, poor suck reflex, high arched palate, and an omega-shaped epiglottis, but otherwise normal larynx, trachea, and esophagus by endoscopic examination. Airway compromise, achalasia, aspiration pneumonitis, and poor nutrition were constant problems. Tracheostomy and gastrostomy were subsequently placed, and the patient's clinical course eventually improved. Early involvement of the otolaryngologist and placement of a tracheostomy and gastrostomy are recommended in those patients with severe otolaryngologic manifestations of AMC.

KEY WORDS — achalasia, arthrogryposis multiplex congenita, gastrostomy, micrognathia, tracheostomy.

INTRODUCTION

Arthrogryposis multiplex congenita (AMC) is not a specific disease. It is a descriptive term encompassing the more than 150 conditions in which multiple congenital joint contractures may exist.[1]

The first clinical description of AMC was published by Otto[2] in 1841, although arthrogryposis, meaning curved joints, was not used until 1923, when Stern[3] coined the term. Although the patient with AMC is generally treated by the orthopedic surgeon, there are important head and neck features that should be recognized by the otolaryngologist–head and neck surgeon.

The following excerpt from his original report shows that in addition to multiple limb and joint deformities, Otto[2] also noted significant head and neck anomalies (Fig 1).

> The face is disfigured in that the nose, though short, protrudes bluntly, the mouth gapes greatly, and the chin is somewhat retracted...The palate is very arched and wide. But the lower jaw is so short and slight that the chin, although well rounded, is positioned too far back, as are the lower alveolar limbus and the tongue.[2]

Since the first report, AMC has been well characterized. Joint rigidity, fusiform or cylindric extremities with absent skin creases, multiple joint dislocations, atrophy or even absence of muscle groups, and intact sensation are the cardinal features of AMC.[4]

The otolaryngologic manifestations of AMC have only infrequently been alluded to in the literature and have rarely been described. In addition to craniofacial anomalies, severe airway compromise, dysphagia, and achalasia with potential for aspiration may coexist with the better-known features of AMC. Here, a case of AMC with severe otolaryngologic manifestations is presented, the literature is reviewed, and management strategies are given.

CASE REPORT

A female infant was born on April 6, 1987, at 39 weeks' gestational age to a 29-year-old, otherwise healthy gravida 3 para 3 mother. Delivery was by cesarean section for breech presentation. Prenatal care was limited, but polyhydramnios was suspected. The delivery was uncomplicated, and Apgar scores at 1 and 5 minutes were 6 and 7. At birth, the infant was noted to have upper and lower extremity deformities. She developed respiratory distress soon after delivery, requiring intubation. After her condition was stabilized, she was transferred to our neonatal intensive care unit.

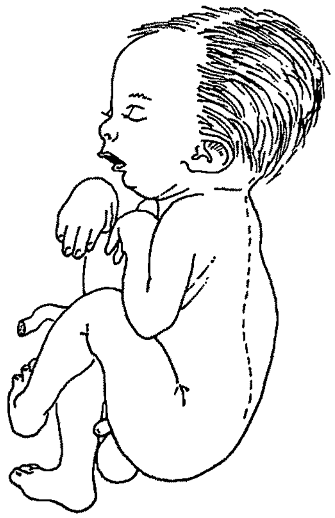

Fig 1. Infant with flexion contractures of upper and lower extremities and micrognathia. (Reprinted with permission.[2])

From the Division of Otolaryngology, Southern Illinois University School of Medicine, Springfield, Illinois.

Presented at the meeting of the American Broncho-Esophagological Association, San Francisco, California, April 3-4, 1989.

REPRINTS — Alberto N. Laureano, MD, SIU School of Medicine, Division of Otolaryngology, PO Box 19230, Springfield, IL 62794-9230.

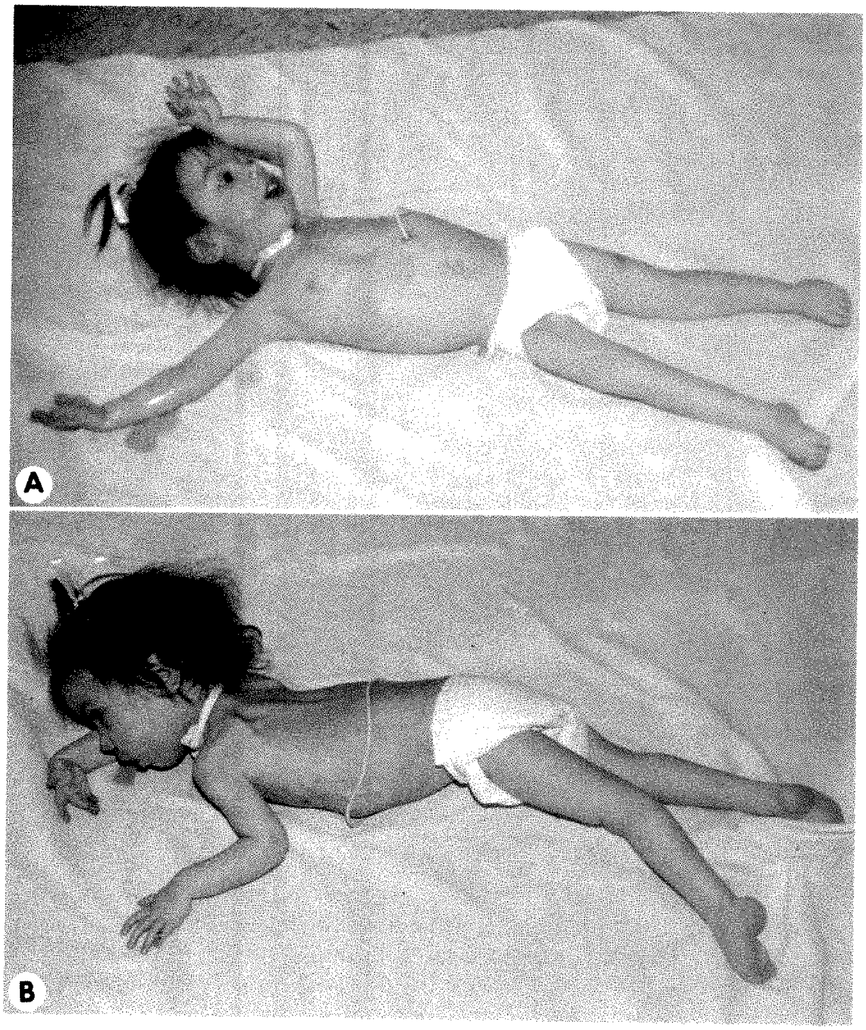

Fig 2. Patient with micrognathia, expressionless face, tracheostomy, gastrostomy, and limb deformities. A) Supine position. B) Prone position.

Initial evaluation revealed a 3,500-g intubated infant whose respirations were spontaneous but shallow. Significant examination findings included micrognathia, a high arched palate, poor suck reflex, prominent hyperextension deformities at the metacarpophalangeal joints, wrist flexion contractures bilaterally, a left elbow flexion contracture, poor passive extension and adduction at the shoulders bilaterally, lack of flexion at the knees, and equinovarus foot deformities (Fig 2). The child was presumed to have AMC, and the pediatric orthopedic surgery service was consulted. A diagnosis of AMC was confirmed, and plans for therapy were made.

The baby was extubated on hospital day 12, but because of inability to clear secretions and because micrognathia made pulmonary toilet difficult, she became intermittently obstructed and then bradycardic. She also developed bilateral pneumonias, proved secondary to achalasia and aspiration by upper gastrointestinal series and gastric milk emptying studies. Reintubation was performed, and the otolaryngology service was consulted.

Examination at that time revealed the previously mentioned micrognathia and high arched palate. Her face was expressionless. No cleft was detected. Endoscopic examination revealed copious pooling of secretions; an omega-shaped epiglottis; an anatomically normal-appearing larynx, trachea, and esophagus; and normal true vocal cord excursion. We recommended and subsequently performed tracheostomy. A gastrostomy was also placed by the general surgery service because of persistent dysphagia and poor nutrition, and as an aid in preventing aspiration.

She subsequently improved and was discharged at 3 months of age. She was readmitted several months later with aspiration pneumonia. This was treated aggressively, but the child's condition deteriorated. She subsequently improved after a long hospitalization and was sent to a children's home for long-term care with tracheostomy and gastrostomy tubes still in place.

ETIOLOGY

The causes of AMC can be separated into four categories: 1) neurogenic, resulting from peripheral and/or central nerve dysfunction; 2) myopathic, re-

TABLE 1. CONGENITAL ANOMALIES ASSOCIATED WITH ARTHROGRYPOSIS MULTIPLEX CONGENITA

Otolaryngologic anomalies
- Cleft palate and high arched palate
- Hyperostosis frontalis
- Insufficiency of laryngeal musculature
- Tracheoesophageal fistula
- Esophageal atresia
- Hypertelorism
- Micrognathia
- Möbius' syndrome
- Klippel-Feil syndrome
- Low-set ears

Other anomalies
- Impaired intelligence
- Meningomyelocele
- Glaucoma and cataract
- Spina bifida
- Other spinal anomalies (eg, scoliosis, kyphosis, sacral agenesis)
- Congenital heart defects
- Hypoplastic lungs
- Renal anomalies
- Cryptorchidism
- Labial and scrotal defects
- Intestinal abnormalities
- Inguinal hernias
- Polydactyly, clinodactyly, syndactyly
- Carpal fusion
- Absence of patella

Information from Hall,[1] Thompson and Bilenker,[4] Brown et al,[5] and Epstein and Wittenberg.[9]

sulting from muscular dysfunction, degeneration, or dystrophy; 3) those resulting from abnormal connective tissues or joints; and 4) restrictive, in which there is decreased space for fetal movement.[1] The most common cause is neurogenic, accounting for approximately 90% by some reports.[5] All cases have in common decreased intrauterine fetal movement. It is this hypomobility that is thought to cause AMC, since a certain amount of intrauterine movement is necessary for normal growth and development of joints and limbs. Spontaneous fetal movement has been detected as early as the seventh week of gestation and prior to maternal awareness of quickening. It is this relatively undetected movement that is thought to be important in joint development.[6]

It has been shown that a variety of factors, including certain mutagenic agents, mitotic abnormalities, toxic chemicals or drugs, hyperthermia, neuromuscular blocking agents, and mechanical immobilization, play a role in AMC by affecting intrauterine movement. These mediators act by one of the above mechanisms to affect the joint. In the end, the joint is compromised, since a loss of muscle mass and subsequent collagenic response leads to contraction and fixation.[6]

Brown et al[5] and others have found degeneration of the anterior horn cell columns in the cervical and lumbar enlargements to be the predominant pathologic change in the more common neurogenic AMC. Changes resulting from meningoceles, myeloceles, and microgyria and cortical atrophy have also been implicated in neurogenic AMC.[5,7,8]

No genetic pattern of predisposition has been demonstrated in the neurogenic form. On the other hand, the much less common myopathic form may show an autosomal recessive pattern.[8]

LITERATURE REVIEW

Unlike the myopathic form, neurogenic AMC is associated with other congenital anomalies. Table 1[1,4,5,9] shows frequently reported anomalies associated with AMC. Otolaryngologic manifestations of AMC have rarely been described.

Temporomandibular joint (TMJ) involvement in AMC has been reported, first by Heffez et al,[10] then by Epstein and Wittenberg.[9] In each case, physical examination findings included micrognathia, high arched palate, and some degree of trismus. The primary treatment proposed in these cases was a surgical approach to the TMJ.[9,10]

In 1973, Cohen[11] reported two patients with AMC associated with laryngeal muscle palsy and subsequent vocal cord paralysis. In each case, vocal cord paralysis resulted in stridor and then airway compromise. Tracheostomy was required in both. Arytenoidectomy was then performed electively, resulting in each patient in an adequate airway and improved speech capability.[11] It should be noted that laryngeal paralysis is not typically seen in AMC. Cricoarytenoid joint fixation was not the cause of laryngeal paralysis in these cases.

In 1976, Cohen and Isaacs[8] reviewed 37 cases of AMC. Nine had otolaryngologic manifestations resulting from the neurogenic form of AMC. Six of nine patients had a Pierre Robin–like syndrome. Seven had severe dysphagia and aspiration pneumonitis. Five of these patients with severe aspiration problems had voice changes, and three of these required tracheostomy to relieve laryngeal obstruction and prevent aspiration. One patient had TMJ disease with significant trismus. Two patients had expressionless facies, pharyngeal paralysis, absent gag reflexes, and inability to protrude their tongues. Three patients had narrowing on laryngeal examination. Esophagoscopy in these patients revealed marked hypertrophy of the cricopharyngeus and upper third of the esophagus.

Only two of the nine patients with otolaryngologic manifestations of AMC were alive at the time of the review of Cohen and Isaacs.[8] Severe dysphagia and subsequent aspiration pneumonitis proved to be a constant nemesis to these patients and was the leading cause of death. Autopsies were performed on six of the seven who died, revealing normal pharyngeal and laryngeal musculature. The cricoarytenoid joints were also found to be normal. Cohen and Isaacs therefore proposed that central

TABLE 2. COMPREHENSIVE CARE TEAM

Developmental pediatrician	Social worker
Neurologist	Psychologist
Geneticist	Educator
Orthopedist	Orthotist
Nurse clinician	Rehabilitation engineer
Physical therapist	Otolaryngologist
Occupational therapist	

Modified from Thompson and Bilenker.[4]

nervous system dysfunction caused dysfunction of the tongue, palate, pharynx, and larynx in these patients, resulting in severe dysphagia and aspiration pneumonitis. Since these otolaryngologic difficulties caused the demise of close to 20% of the AMC patients they studied, Cohen and Isaacs[8] concluded that tracheostomy and gastrostomy are essential in those patients with otolaryngologic manifestations of AMC in order to ward off potential fatal complications.

DISCUSSION AND CONCLUSIONS

Since the cause of AMC is multifactorial, no effective means of prevention is currently available. Thus, supportive management is the standard of care in AMC. Orthopedic surgeons have traditionally taken a primary role in this regard, since their early involvement is necessary in order to achieve the best functional results in each case. However, the many diagnostic possibilities, associated disorders, complicated genetics and potential counseling problems, and need for long-term follow-up in AMC make it impossible for any one individual to effectively manage these patients. Thompson and Bilenker[4] have developed the concept of a comprehensive care team, a group of physicians and paramedical personnel in one clinic setting, for the management of AMC (Table 2[4]). In their system, the pediatrician serves as coordinator.

Since head and neck anomalies are quite common in neurogenic AMC, and since neurogenic AMC comprises about 90% of all those with AMC, most AMC patients could potentially demonstrate otolaryngologic manifestations.

Our patient, along with those patients in the series of Cohen and Isaacs,[8] illustrates how difficult the management of severe head and neck manifestations of AMC can be. Severe dysphagia, recurring aspiration pneumonitis, and poor nutrition were constant problems. Since, by examination, there was no obvious deformity of pertinent structures, we concur with the hypothesis of Cohen and Isaacs that central nervous system dysfunction causes these symptoms. In spite of early placement of tracheostomy and gastrostomy tubes, our patient's hospital course was quite protracted. Without early aggressive surgical intervention, she certainly would not have survived.

We therefore recommend that in cases of AMC associated with otolaryngologic manifestations, and in particular those with airway compromise, severe dysphagia, or aspiration, that the otolaryngologist be included in the team approach to management.

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LARYNGEAL AND LARYNGOTRACHEOESOPHAGEAL CLEFTS: ROLE OF EARLY SURGICAL REPAIR

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An uncommon congenital anomaly of the developing aerodigestive tract is the congenital laryngeal cleft and its extension, the congenital laryngotracheoesophageal (LTE) cleft. Because of the subtle findings sometimes seen with clefts confined to the larynx, the diagnosis may be difficult. The potential problems of airway obstruction and repeated aspiration frequently associated with laryngeal and LTE clefts mandate early surgical repair. Over the past 3 years, 14 patients with congenital laryngeal or LTE clefts have been managed at Children's Hospital Medical Center, Cincinnati, Ohio. This report details our experience and philosophy regarding the diagnosis and management of the condition, and presents the histopathologic findings of a case of complete LTE cleft in which surgical repair was delayed and death resulted.

KEY WORDS — aerodigestive tract, congenital laryngeal cleft, congenital laryngotracheoesophageal cleft.

Congenital laryngeal and laryngotracheoesophageal (LTE) clefts are uncommon conditions that were not described until 1792[1] and not successfully corrected surgically until 1955.[2] Although Pettersson[2] divided laryngeal clefts into three basic types, Armitage[3] presented an alternative classification scheme in 1984 that more completely describes the entity. In Armitage's system, Pettersson's type I cleft, a laryngoesophageal fissure in which only the cricoid is split, is divided into three subgroups. In type I-A, the only abnormality is absence of the interarytenoid muscles, and there is an intact cricoid cartilage. In type I-B, the interarytenoid muscles are absent and there is a partial absence of the cricoid. In type I-C, the interarytenoid muscles are absent and the cricoid cartilage is incomplete posteriorly. Armitage utilizes Pettersson's classification scheme for type II and III clefts, ie, the type II cleft represents an LTE fissure extending into the trachea, while a type III cleft involves a complete LTE fissure to the level of the carina.

More recently, Benjamin and Inglis[4] proposed a new classification. In their scheme, type I is a supraglottic interarytenoid cleft that is above the level of the vocal cords. Type II is a partial cricoid cleft extending below the level of the vocal cords and partly, but not completely, through the posterior lamina of the cricoid cartilage. Type III is a total cricoid cleft, with or without further extension into a major part of the intrathoracic tracheoesophageal wall.

In distinguishing between those clefts confined to the larynx and those that extend beyond into the trachea and esophagus, it is clear that the type III of Benjamin and Inglis includes both types. A more accurate and precise nomenclature would label clefts confined to the larynx (not extending beyond the cricoid cartilage) as laryngeal clefts and any cleft extending more inferiorly into the trachea and esophagus as an LTE cleft. To avoid confusion and to allow easier comparison with other studies, we have labeled Armitage's type I clefts as laryngeal clefts. Laryngotracheoesophageal clefts are classified as type I (extending into the trachea and esophagus but short of the carina) or type II (extending to the carina).

As noted in the last major review of the literature in 1983,[5] most reports present only isolated case studies with a description of the surgical approach utilized and a review of the literature. These reports stress the difficulty with diagnosis and repair of this condition and the universal morbidity and possible mortality associated with it. However, the various reports do not address fully the role of early surgical intervention in selected cases.[3-21]

We review 14 cases managed at Children's Hospital Medical Center, Cincinnati, Ohio, from July 1, 1985, until June 30, 1988, emphasizing our approach to the diagnosis and management of this condition. The importance of this approach is emphasized in a detailed analysis of one case in which failure to adhere to these standards complicated patient management.

Patient data are summarized in Tables 1 through 3. As noted in Table 2, 13 patients underwent surgical repair for laryngeal or LTE cleft. Of the 10 patients with a laryngeal cleft, 9 were successfully repaired in a single stage through either an anterior laryngofissure (8 patients) or an endoscopic approach (1 patient). One patient with a laryngeal

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TABLE 1. GENERAL PATIENT DATA AND ASSOCIATED ANTENATAL OR PRENATAL EVENTS (N = 14)

Male:female	9:5		
White:black	13:1		
Extent of cleft	Laryngeal	10	
	Armitage I-A		5
	Armitage I-B		0
	Armitage I-C		5
	Laryngotracheoesophageal	4	
	Type I		3
	Type II		1
Bronchopulmonary dysplasia		2	
Polyhydramnios		1	
Prematurity (<36 weeks' gestation)		2	

cleft required two anterior laryngofissures to effect closure. It should be noted, however, that this patient had previously undergone multiple laser procedures for the treatment of presumed subglottic stenosis that was, in fact, esophageal mucosa prolapsed through a cricoid cartilage cleft.

Only one of the three patients with a type I LTE cleft was effectively treated through a single-stage anterior laryngofissure. The other two patients had persistent tracheoesophageal fistulas (TEFs) following the initial surgical repair that necessitated another procedure to repair the fistula. In one of these patients, several prior attempts at closure of concomitant TEF had left the surgical field scarred and relatively devascularized. In the other patient, severe tracheomalacia complicated positioning of the tracheotomy tube following the initial procedure and ultimately led to erosion of the posterior tracheal suture line.

All but one patient have been decannulated successfully, including the three patients with concomitant subglottic stenosis. The child who was not decannulated had a type I LTE cleft repaired successfully through an anterior laryngofissure, but required a tracheotomy for severe tracheomalacia and bronchomalacia. Three children continue to require supplemental gastrostomy feedings. These patients all had repairs of type I LTE clefts and continue to manifest dysmotility of the esophagus that prohibits adequate oral intake.

CASE REPORT

A 2-month-old child was transferred to Children's Hospital Medical Center for the repair of a suspected congenital LTE cleft and laryngeal atresia. She was the product of a 34-week gestation in a 27-year-old primigravida mother. The pregnancy was complicated by polyhydramnios. Delivery was performed by cesarean section shortly after spontaneous rupture of membranes occurred. Birth weight was 2.03 kg, and Apgar scores were 5 and 7 at 1 and 5 minutes, respectively. Respiratory distress was noted in the delivery room, and an emergency tracheotomy was performed after multiple attempts at endotracheal intubation were unsuccessful because of laryngeal obstruction. The arterial blood gas tests that were performed immediately before tracheotomy demonstrated a pH of 6.96, a P_{CO2} of 108, and a P_{O2} of 74 while the infant was breathing 100% oxygen. The chest radiograph at that time demonstrated a right pneumothorax that was subsequently evacuated.

The early prenatal course was very difficult, re-

TABLE 2. ASSOCIATED ANOMALIES, SYMPTOMS AT PRESENTATION, AND SURGICAL APPROACH BY TYPE OF CLEFT (N = 14)

	Laryngeal (n = 10)	*Type I Laryngotracheoesophageal (n = 3)*	*Type II Laryngotracheoesophageal (n = 1)*
Associated anomalies	Vocal cord paralysis Subglottic stenosis (2) Innominate artery compression Tracheomalacia (2) Gastroesophageal reflux (2) Tracheoesophageal fistula Anal stenosis (2) Opitz-Frias syndrome Hypospadias Ureteral reflux	Tracheomalacia Short trachea Gastroesophageal reflux Tracheoesophageal fistula Microgastria Malrotation Opitz-Frias syndrome (2) Hypospadias (2) Hydronephrosis Seizure disorder Hypoplastic digits Hypertelorism	Laryngeal atresia Gastroesophageal reflux Microgastria Pyloric atresia Atrial septal defect
Symptoms at presentation	Apnea Aspiration (6) Dyspnea with exertion Stridor (4) None — incidental finding at operation (3)	Aspiration (3) Dyspnea (3)	Aspiration Dyspnea
Surgical approach	Anterior laryngofissure (9) Endoscopic (1)	Anterior laryngofissure (3)	No surgical procedure

TABLE 3. INDIVIDUAL PATIENT DATA (N = 14)

Pt	*Sex*	*Age at Diagnosis*	*Extent of Cleft*	*Symptoms*	*Concurrent Anomalies*
1	M	14 yr	1 cm, mucosal, without cricoid involvement	Stridor and respiratory distress with exertion	Redundant soft tissue of left aryepiglottic fold; left true vocal cord paralysis; right true vocal cord adducted
2	F	1 yr 4 mo	Through cricoid	Aspiration of liquids only	Subglottic shelves; ureteral reflux, Opitz-Frias syndrome
3	M	Birth	Type I LTE	None	Seizure disorder
4	F	2 yr 1 mo	Mucosal, without cricoid	Aspiration of liquids and solids	None
5	M	8 mo	Through cricoid	Inspiratory stridor, reflux, aspiration	Hemangioma of posterior cervical esophagus, hydronephrosis
6	M	10 mo	Mucosal, without cricoid	Aspiration, inspiratory stridor	None
7	M	2 mo	Mucosal, without cricoid	Aspiration, cyanosis	Hiatal hernia, anal stenosis, innominate artery compression
8	F	2 d	Through second tracheal ring	Aspiration	Hypoplastic fingers, bronchopulmonary dysplasia, gastroesophageal reflux, tracheomalacia, esophageal dysmotility, bronchial stenosis, bronchomalacia
9	M	1 wk	Through third tracheal ring	Aspiration	Opitz-Frias syndrome, hypospadias, hypertelorism, wide anterior fontanel
10	M	1 mo	Through cricoid	Apnea, aspiration	Hyperdynamic posterior tracheal wall
11	M	3 yr	Through cricoid	None	Opitz-Frias syndrome, hypospadias with chordee, cerebral palsy, tracheomalacia
12	F	14 d	Type II LTE, to 1 cm from carina	Respiratory distress, aspiration, cyanosis	Laryngeal atresia, atrial septal defect, aortic stenosis, pyloric atresia
13	M	14 yr	1 cm, mucosal	None	Subglottic stenosis
14	F	2 yr 7 mo	1 cm into cricoid	Aspiration	Trisomy 21, tracheoesophageal fistula, bilateral vocal cord paralysis, subglottic stenosis

LTE — laryngotracheoesophageal.

quiring vasopressor support from day 3 of life through day 7. Echocardiography noted an atrial septal defect with left-to-right shunting and a mild degree of aortic stenosis. On day 9 of life, a gastroduodenostomy was performed because of pyloric atresia. A subsequent barium esophagram showed an extensive congenital LTE cleft with significant gastroesophageal reflux. An unsuccessful fundoplication was performed, and the child subsequently underwent a gastric division with double gastrostomies.

Artificial ventilation continued until day 28 of life, when the child was weaned to room air. She did well for approximately 3 weeks, until she developed increasing oxygen requirements. At approximately 2 months of age, the child developed persistent respiratory distress, at which time it was noted that she had hyperinflation of the right lung with atelectasis of the left lung. Mechanical ventilation was again instituted, and the child had several endoscopic procedures in an effort to improve the ventilatory status. At this point, the patient was transferred to our institution because of the perceived need for surgical correction, intensified by the patient's deteriorating respiratory status.

At the time of transfer, the child weighed 2.7 kg. She had an axillary temperature of 38.6°C with a pulse of 140 beats per minute. The blood pressure was 116/76. The child had no external anomalies visible, but had a tracheotomy and dual gastrostomies present. A grade II/VI systolic murmur was heard along the left sternal border. Peripheral pulses were good. The abdomen was not distended. A chest radiograph demonstrated hyperaeration of the right middle lobe and right lower lobe with atelectasis of the right and left upper lobes. A complete blood count revealed a normal hematocrit and hemoglobin, but a white blood cell count of 16,000/mm^3 with 91% neutrophils.

Mechanical ventilation was continued, and the child was placed on a regimen of vancomycin and cefuroxime sodium for treatment of pneumonia. The child stabilized enough to have an endoscopic procedure performed, at which time the diagnosis of laryngeal atresia (Fig 1) and a type II LTE cleft (Fig 2) was made. Because of the length of the cleft, the child's tracheotomy tube fell into the esophagus readily. As a result, the child had episodes of marked oxygen desaturation and hypoventilation.

Following the initial diagnostic endoscopy, the child suffered progressive respiratory embarrassment, in part due to the accumulation of mucous plugs in the trachea and bronchi. There were episodes of both oxygen desaturation and carbon dioxide retention requiring increasing ventilatory pressures and rate using 100% oxygen. Planned surgical correction was cancelled because of the unstable respiratory status. In the face of continuing deteriora-

TABLE 3 (continued). INDIVIDUAL PATIENT DATA (N = 14)

Treatment	*Time for Resolution of Symptoms*	*Removal of Tracheotomy Tube*	*Removal of G-Tube*
Tracheotomy, two-layer closure, laryngofissure	2 mo	2 mo	—
G-tube, Nissen fundoplication, tracheotomy, two-layer closure, laryngofissure	3 wk	3 wk	G-tube still in
Tracheotomy, tracheoesophageal fistula repair via lateral approach x4, laryngotracheoplasty, G-tube	Tolerating all but liquids	1 mo	G-tube still in
Endoscopic repair	1 mo	—	—
G-tube, Nissen fundoplication, tracheotomy, two-layer closure, laryngofissure	3 mo	3 mo	—
G-tube, tracheotomy, three-layer closure, laryngofissure	2 mo	2 mo	2 mo
Nissen fundoplication, two-layer closure, laryngofissure	1 mo	1 mo	—
Gastric division, tracheotomy, two-layer closure, laryngofissure, tracheoesophageal repair (lateral) 3 weeks later	3 mo	1 mo	G-tube still in
G-tube, tracheotomy, three-layer closure, laryngofissure	Without swallowing problems postoperatively	Still tracheotomized with 00 Shiley tube	4 mo
Tracheotomy, laryngofissure, three-layer closure	2 mo	2 mo	—
Laryngofissure, two-layer closure, revision laryngofissure and two-layer closure of superior half, anterior keel	4 mo	4 mo	—
Tracheotomy, G-tube, Nissen fundoplication, gastric division, no repair (patient died)	—	—	—
Two-layer closure, laryngofissure	3 mo	3 mo	—
G-tube, two-layer closure, laryngofissure, laryngotracheoplasty with posterior costal cartilage graft	6 mo	16 mo	16 mo

G-tube — gastrostomy tube.

tion of the respiratory status, a consensus decision was made to withdraw the infant from the ventilator, and she subsequently died on day of life 70.

DISCUSSION

The infant presented had a rare, clinically well-defined major anomaly of the larynx and upper trachea that could be categorized during a postmortem examination. The basic defect consisted of collagenous atresia of the larynx and upper trachea with a posterior midline cleft of the larynx and trachea that was continuous with the esophagus. The proximal trachea (below the solid laryngeal cartilage mass) was atretic for a short distance and beyond that was patent with a normal lumen, but communicated with the esophagus through a long cleft. In addition, the right pyriform sinus ended in a blind pouch (Fig 3). The region of the bifurcation of the trachea was slightly anomalous in the pattern of branching and was not obviously narrow, but was obstructed by mucus. Mucous plugs were also prominent in the major and minor bronchi and were responsible for an irregular pattern of atelectasis and acute obstructive emphysema. Contributing to the tendency to mucous plug formation was the extensive mucin gland hyperplasia in the surface epithelium of many of the major bronchi. An anomalous retroesophageal right subclavian artery was identified, but it is problematic whether it was obstructive.

The tracheal lining exhibited severe diffuse necrotizing changes consistent with aspiration of low-pH gastric contents. Acute aspiration-type pneumonia with hyaline membranes was present in some areas. The presence of ulcerating reflux-type esophagitis would suggest that significant reflux was occurring and that this was the most likely basis for the severe tracheitis and aspiration pneumonia. Thus, it would seem as if the gastric division procedure was somewhat ineffective. In fact, the proximal gastric fundic mucosa is known to be endowed with secretory cells, including parietal cells, that might respond to circulating kinins activated by distal feedings.

This child had multiple congenital anomalies in addition to the complex anomaly of foregut septation, including an anomalous origin of the right subclavian artery, anomalous branching of the distal trachea, pyloric atresia, and extensive pancreatic ectopia in the wall of the pylorus. In addition, the child had an atrial septal defect and a mild degree of aortic stenosis.

As noted previously, laryngeal and LTE clefts are an uncommon condition associated with a high mortality rate. In a review by Roth et al[5] of 85 cases in 1983, an overall mortality rate of 46% was found for this condition. When each type of cleft was looked at specifically, there was found to be a mortality rate of 43% (13/30) for laryngeal cleft, 42%

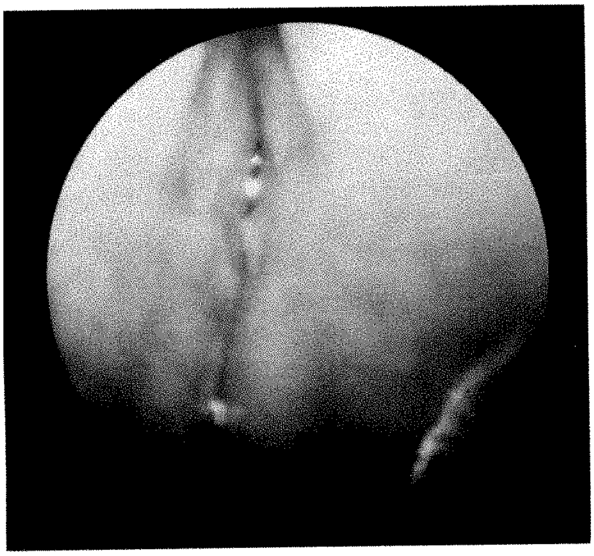

Fig 1. Laryngeal atresia that prevented intubation when child experienced respiratory distress in delivery room.

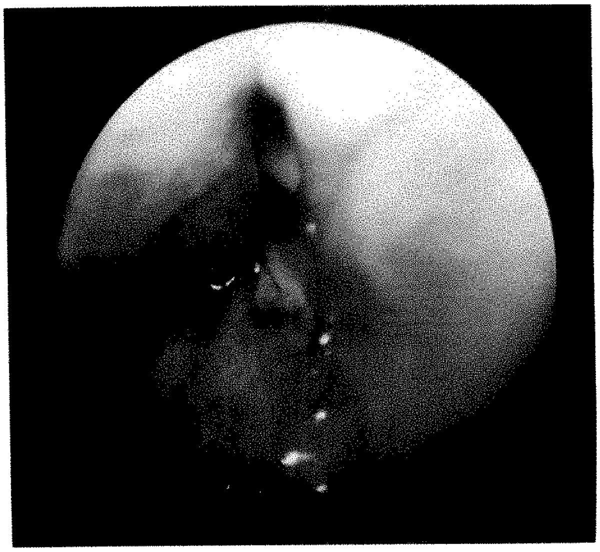

Fig 2. Tracheotomy tube noted anteriorly through cephalic portion of congenital laryngotracheoesophageal cleft.

(13/31) for type I LTE cleft, and 93% (13/14) for type II LTE cleft. Of the patients who died, 67% had other serious congenital malformations.

In the case presented, the child had several radiographic procedures to assist in the definition of the problem, but did not have an endoscopic procedure performed for several months. Even though the patient had undergone a tracheotomy and a gastric division with double gastrostomy, without a definitive diagnostic procedure to establish the full extent of the child's anatomic problem, surgical repair could not be effected. Shortly before transfer to our institution, the patient developed progressively worsening respiratory status that ultimately militated against surgical repair. This course suggests that early diagnosis and repair are mandatory to prevent irreversible pulmonary damage from continued aspiration.[15]

In almost all cases of laryngeal cleft, there should be minimal morbidity and mortality. Though these patients may experience some temporary pulmonary problems secondary to aspiration, these are often readily controlled and are usually not life-threatening. However, type I and type II LTE clefts are associated with a significant mortality in addition to an almost universal morbidity.[5,11] In fact, there have been only three survivors with type II LTE cleft reported in the literature.[12] Separation of the common aerodigestive passage into distinct respiratory and alimentary tracts may be life-saving. Endoscopic examination is essential to establish the diagnosis of laryngeal or LTE cleft in a child with symptoms such as stridor, cyanosis with feeding, and persistent aspiration. Then, once the patient's condition is stabilized — and this may involve a gastric division with double gastrostomies as well as a tracheotomy — definitive surgical repair should be undertaken at the earliest possible time. If repair is delayed, life-threatening pulmonary complications may ensue that prohibit surgical repair and ensure the ultimate demise of the patient.

While some authors discount the necessity of repairing laryngeal clefts,[21] identification of such an abnormality in a symptomatic patient warrants surgical repair. Essentially all such lesions can be approached successfully through an anterior laryngofissure (Fig 4), although very small clefts might be repaired endoscopically.[21] Should a tracheotomy be necessary, cannulation likely will be of short duration and, in certain cases, might be avoided altogether. As noted above, we repaired all but one of our patients through an anterior laryngofissure. This approach appears to be satisfactory in almost all laryngeal and type I LTE clefts, offering the advantage of excellent exposure that provides for the precise trimming of esophageal mucosa and minimizes risk to the recurrent and superior laryngeal nerves. Adverse effects on laryngeal development and stability do not appear to be a problem.[5,6,10,21] In patients with type II LTE clefts, a lateral cervical approach combined with a thoracotomy as described by Cotton and Schreiber[9] is preferable.

The philosophies that have been established for surgical repair of laryngeal and LTE clefts can be used only as general guidelines.[5,6,9] Because of the large number of concurrent anomalies found in patients with laryngeal and LTE clefts, the surgical approach may be dictated by the associated findings.[5,19] Specifically, tracheotomy may be contraindicated during the definitive surgical repair when there is significant tracheomalacia, since there may be erosion of the posterior suture line with a subsequent TEF or persistent cleft. In this situation, nasotracheal or orotracheal intubation for a period of time in a paralyzed child may obviate the need for a tracheotomy.[6] Similarly, should a TEF result, inter-

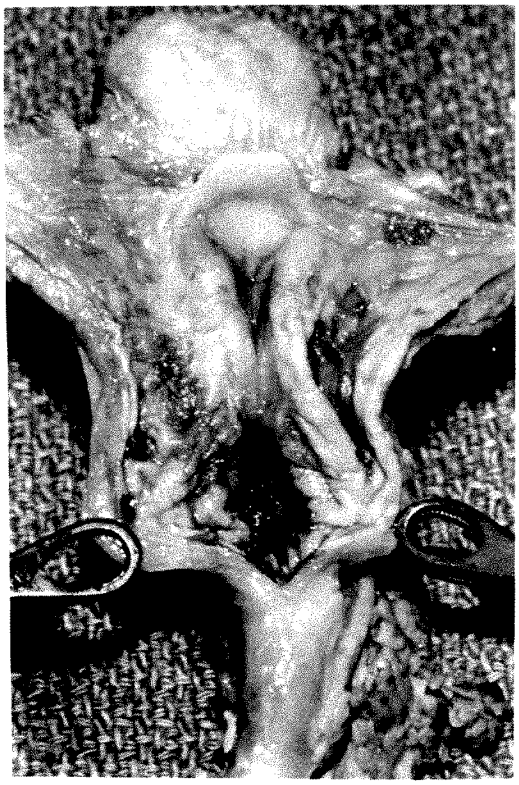

Fig 3. Gross specimen showing congenital laryngotracheo-esophageal cleft with right pyriform sinus ending as blind pouch.

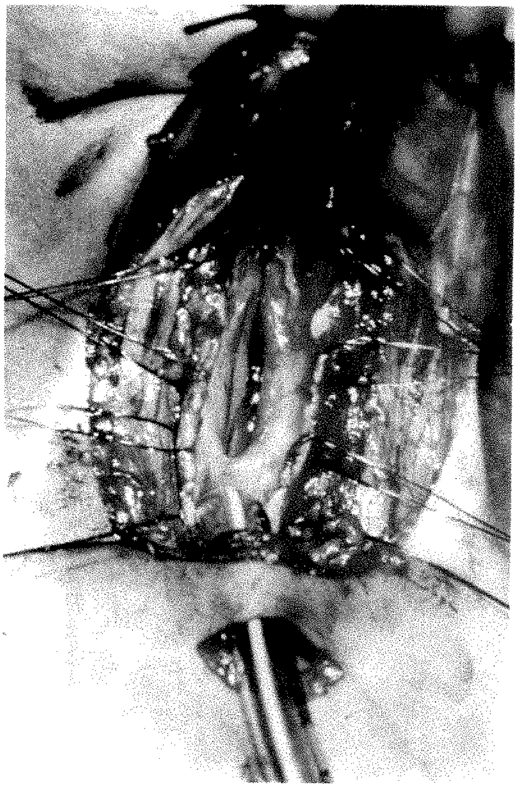

Fig 4. Preferred surgical approach for most laryngeal and type I laryngotracheoesophageal clefts, ie, through anterior laryngofissure.

position of a superiorly based sternocleidomastoid muscle flap between the trachea and esophagus is effective in reinforcing the surgical repair. When this type of flap is used, it should be sutured to structures in the contralateral side of the neck in order to secure its position.

Postoperative evaluation of these patients should include both endoscopic and radiographic studies. Most, if not all, of these patients have incoordination of their swallowing mechanism following surgical repair. Because of this, a barium esophagram will frequently demonstrate continued aspiration that could be interpreted as incomplete closure of the laryngeal or LTE cleft, when in fact it may be a reflection of the patient's esophageal dysmotility. Therefore, visual confirmation of the integrity of the surgical repair is essential to provide conclusive evidence. In addition, either a barium esophagram or a radionuclide scan may demonstrate gastroesophageal reflux. If this is demonstrated, fundoplication is recommended.[12]

As noted in the Tables presented, 21% of the patients in our series had no symptoms referable to a laryngeal cleft, and their laryngeal or LTE clefts were discovered either incidentally or following multiple surgical procedures for a condition that was incorrectly diagnosed. One must consider a laryngeal cleft in any patient with an irregular posterior subglottic stenosis. In reality, this may represent prolapse of esophageal mucosa through an incomplete cricoid cartilage.[8,13,22]

Presentation of a large series of patients with laryngeal and LTE clefts would help clinicians learn to recognize the signs and symptoms of this congenital abnormality. Because the condition is uncommon, the diagnosis is frequently missed and therapeutic intervention delayed. Only through an aggressive surgical approach can the morbidity and mortality associated with laryngeal and LTE clefts be decreased.

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PAN AMERICAN ASSOCIATION OF OTORHINOLARYNGOLOGY–HEAD AND NECK SURGERY

The XXII Congress of the Pan American Association of Otorhinolaryngology–Head and Neck Surgery will be held November 23-27, 1990, in Catagena, Colombia. For further information, contact Pedro Blanco, President, Pan American Congress, Hospital Universitario del Valle, 3er Piso Servicio de Otorrinolaringologia, Cali, Colombia.

Ann Otol Rhinol Laryngol 99:1990

LARYNGEAL AMYLOIDOSIS IN A CHILD

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A 14-year-old girl developed progressive hoarseness and breathing difficulty due to a mass in the subglottic larynx. A biopsy specimen obtained at direct laryngoscopy showed localized aggregates of amyloid. The lesion was excised completely with a carbon dioxide laser. This is the second case of laryngeal amyloidosis in a child reported in the English-language literature.

KEY WORDS — amyloidosis, laryngeal amyloid, subglottic mass.

INTRODUCTION

Amyloid deposits in tissue were first identified by von Rokitansky[1] in 1842. Virchow[2] in 1851 was first to use the word amyloid to describe the substance, when he noted an appearance and staining properties similar to starch. Amyloidosis of the larynx was first reported by Borow in 1873.[3] Since then, approximately 300 cases have been reported, the largest series being 235 cases reviewed by McAlpine and Fuller in 1964.[4] To date, only 2 have been identified in the pediatric age group.[4,5] We present another case of laryngeal amyloid in a child and review the current understanding of this disease.

CASE REPORT

A 14-year-old girl had been hoarse since she was a small child. For the past 2 to 3 years she had also developed increased breathing difficulty, particularly during physical exertion or when ill with a cold. At the time of her initial evaluation she was quite hoarse. Stridor was audible when she breathed deeply. Indirect examination of the larynx showed a smooth, mucosa-covered lesion in the anterior subglottic region. The remainder of her examination produced normal findings. A computed tomographic scan of the larynx showed a 1.5-cm nonenhancing mass in the anterolateral aspect of the right subglottic larynx that extended into the proximal trachea (see Figure, A).

At direct laryngoscopy a pale, smooth, mucosa-covered lesion was seen that extended from the anterior commissure and inferomedial aspect of the anterior right vocal fold into the supraglottic larynx. Frozen sections of multiple biopsy specimens contained amorphous material in the submucosa suspicious of amyloid. The lesion then was excised completely with the carbon dioxide laser. There has been no recurrence of symptoms in over 12 months of follow-up.

Hematoxylin and eosin staining of the biopsy material showed abundant areas of acellular, amorphous, eosinophilic material within the lamina propria underlying normal laryngeal mucosa. The basement membrane was intact (see Figure, B). Congo red staining imparted a homogeneous reddish color to the amyloid. Areas of perivascular amyloid were also present. Amyloid aggregates were seen as a green birefringence with dichroism under polarized light.

DISCUSSION

Amyloid deposits in the larynx account for less than 1% of all benign tumors of the larynx.[6] The larynx, however, represents the most common site for isolated amyloid, not only of the respiratory tract, but also of the body in general.[4,7] Less common respiratory sites include the trachea, base of the tongue, nasal cavity, and pharynx. Patients usually present with hoarseness and breathing difficulty. Hemoptysis is uncommon. Peak incidence is between the ages of 40 and 60 years. Men are affected three times as often as women.[6]

Laryngeal amyloid appears as a waxy yellowish mass under intact epithelium. The most common sites of involvement are the true vocal cords, followed by the false vocal cords, the aryepiglottic folds, and the subglottic region.[8] The four patterns of deposition described in the larynx are 1) amorphous masses, 2) deposits in vessel walls, 3) deposits in the basement membranes of mucoserous glands, and 4) hyalinized rings in adipose tissue.[9] Areas likely to contain coexistent amyloid include the trachea, bronchi, and tongue.[4]

Histologic sections of tissue with amyloid can be stained selectively with Congo red, which imparts a green birefringence and dichroism to the amyloid when it is viewed under polarized light. Other useful stains include methyl violet, which produces a pink-violet metachromasia in amyloid, and thioflavine-T, which causes amyloid to fluoresce under ultraviolet light.[8] The staining properties of amy-

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Presented at the meeting of the American Broncho-Esophagological Association, San Francisco, California, April 3-4, 1989.

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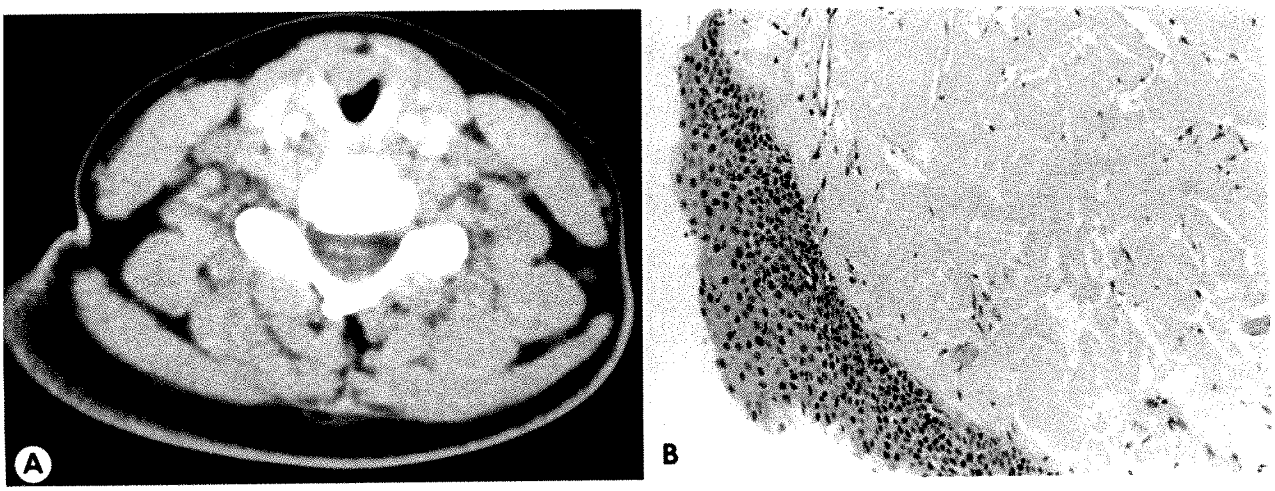

A) Computed tomographic scan of larynx at level of inferior thyroid cornua and cricoid cartilage showing right anterior mass with 50% obstruction of subglottic airway. B) Permanent section showing substantial areas of cellular, amorphous eosinophilic material within lamina propria underlying normal laryngeal mucosa (H & E, original x160). Basement membrane is intact.

loid are due to a β-pleated sheet configuration of the fibrils seen on x-ray crystallography. These fibrils constitute 95% of the amyloid substance, the remaining 5% being a pentagonal subunit identified as an α glycoprotein.

Amyloid fibrils, previously thought to be identical in all forms of amyloid, are now known to arise from a number of unrelated precursors. Glenner[10,11] in 1980 classified the various types of fibrils as

1. AL. The N-terminal sequence of immunoglobulin light chains found in primary and organ-limited amyloids such as laryngeal.
2. AA. An unidentified semiconstant sequence polypeptide found in secondary forms.
3. AF. Prealbumin found in familial forms.
4. AS. Prealbumin found in senile deposits.
5. AE. Hormonal precursors of APUD tumors.

In 1956 Symmers[12] proposed the original classification of the types of amyloidosis, including the primary, secondary, localized, and familial forms and those associated with multiple myeloma. The current classification, proposed by Glenner in 1980, uses the knowledge of fibrillar composition and clinical presentation as a means of classification.[10,11] Glenner's categorization of the β-fibrilloses (amyloidoses) is given in the Table.[10,11] Within this new classification, amyloid of the larynx is classified as organ-limited and immunocyte-derived. Its fibril subunit is of the AL type and therefore derived from the N-terminal subunit of either ϰ or λ light chains.

The clinical differential diagnosis of laryngeal amyloid includes verrucous carcinoma, myxomatous polyp, leukoplakia, squamous carcinoma, and ductal cysts.[13] Histologically, a hyalinized laryngeal polyp can appear to be similar to laryngeal amyloidosis.

A number of authors advocate an extensive workup for systemic disease when amyloid is identified in the larynx.[5,9,14-17] Of the methods described, a fine needle aspiration of abdominal fat is an accurate and relatively atraumatic method of identifying generalized amyloidosis.[18] However, since the association of laryngeal amyloid with generalized amyloidosis is extremely rare, some authors believe that an extensive workup may not be warranted.[13]

Treatment of laryngeal amyloid is surgical excision. Small lesions are easily excised endoscopically, but large lesions may require a laryngofissure approach.[6] Diffuse laryngeal involvement will frequently require multiple limited procedures for excision to avoid postoperative stenosis.[13] Laser excision has also been advocated.[19,20]

CONCLUSIONS

Amyloid deposits within the larynx are uncommon, particularly in the pediatric population. Laryngeal involvement in the systemic forms is extremely rare. Nevertheless, it is important for the otolaryngologist–head and neck surgeon to be familiar with these lesions, to be able to recognize them, and to respond appropriately when they are diagnosed. The treatment of these lesions is local surgical excision. With complete excision, the potential for cure is excellent.

BETA-FIBRILLOSES

- Acquired systemic
  - Associated with immunocyte dyscrasias (previous primary forms and amyloid associated with multiple myeloma, Waldenström's disease, heavy chain disease)
  - Reactive systemic (all previous secondary forms)
  - Heredofamilial types
- Organ-limited
  - Immunocyte-derived (respiratory tract [laryngeal], urinary tract)
  - Senile (cardiovascular, cerebral, cutaneous)
- Localized deposition
  - APUD amyloid
  - Plasmacytoma-associated

Information from Glenner.[10,11]

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY
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A course entitled Functional Endoscopic Sinus Surgery — The Messerklinger Technique will be held July 5-7, 1990, in Graz, Austria. For further information, contact Prof H. Stammberger, MD, University ENT-Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria.

Ann Otol Rhinol Laryngol 99:1990

EFFECT OF LARYNGEAL STENTING IN A RABBIT MODEL

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A short length of oversize endotracheal tube was sutured in the undamaged subglottis of 22 rabbits to explore the effect of laryngeal stents. The stent was secured to lie beneath the vocal cords. The histologic changes were minimal irrespective of the type of tube used and how long it remained in situ. These findings are consistent with the theory that tube movement is necessary to produce stenosis and are encouraging given the widespread use of stents in pediatric laryngeal reconstruction. The role of gastric acid in producing subglottic stenosis is discussed.

KEY WORDS — larynx, stenosis, stent, subglottis.

INTRODUCTION

The current treatment in most centers of acquired subglottic stenosis in infants no longer depends on a passive policy of tracheotomy and awaiting laryngeal growth, but has changed to a more active policy in which reconstructive surgery is employed.[1,2] This allows earlier decannulation with a reduction in tracheotomy-related morbidity. An alternative approach would be to try to prevent the immature scar tissue from late scar tissue contracture.

The subglottic narrowing measured prior to initial tracheotomy is often worse when assessed 3 or 6 months later. This may be due to the lumen's being "splinted" by the long-standing endotracheal tube at the time of the initial assessment, or it may be due to concentric fibrous contracture. If so, an indwelling stent placed at the time of tracheotomy could reduce or remove the need for later surgical reconstruction. The use of a stent at this site would be analogous to its use in meatoplasty or in choanal atresia.

The idea of long-term stenting is not new,[3-5] but as the initial damage is thought to relate to movement of the tube within the larynx, any stent should be separate from the tracheotomy tube.

There is histologic evidence[6] that re-epithelialization of early lesions can occur, a fact that is exploited in the operation of anterior cricoid split.[7] The present study looks at one way of securing such a stent and examines histologically the damage caused by leaving two types of stent in situ for various periods. The technique employed is derived from previously reported animal experiments.[8-11]

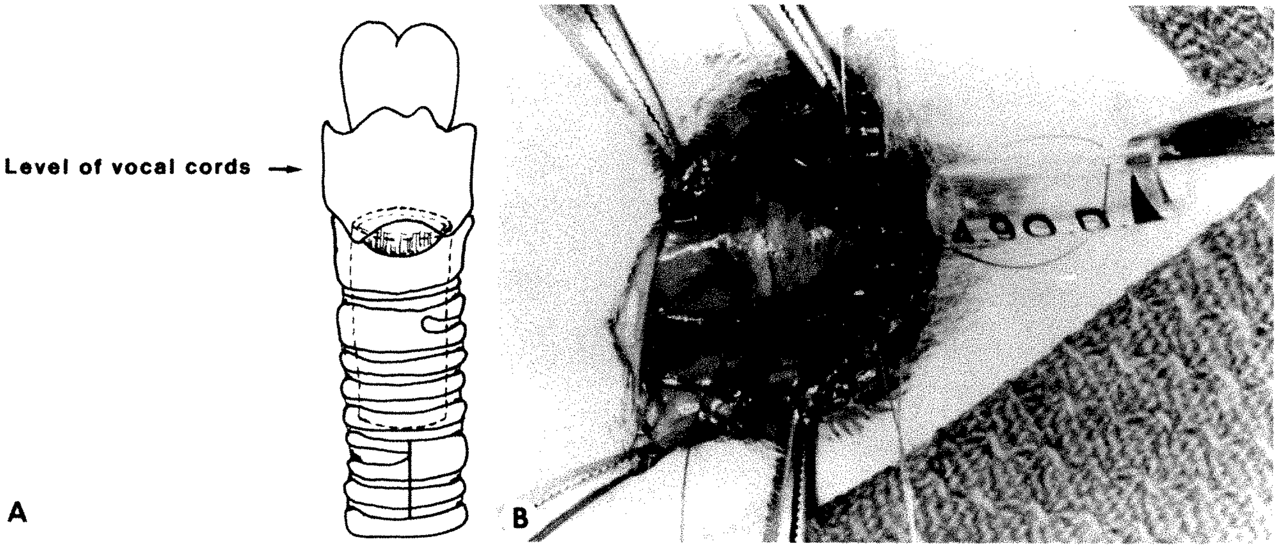

Fig 1. Stent being inserted through low vertical incision and secured to lie beneath vocal cords. A) Diagram. B) Photograph.

From the Department of Otolaryngology, Hospital for Sick Children, London, England (Albert), the Department of Otolaryngology, Children's Hospital Medical Center, Cincinnati, Ohio (Cotton), and the Department of Pathology, Norfolk and Norwich Hospital, Norwich, England (Conn). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Cincinnati, Cincinnati, Ohio.

Presented at the meeting of the American Broncho-Esophagological Association, San Francisco, California, April 3-4, 1989.

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TABLE 1. HISTOLOGIC ABNORMALITIES IN SUBGLOTTIS OF ANIMALS KILLED IMMEDIATELY

Animal	*Time Stent Was in Larynx (wk)*	*Normal Tissue*	*Polymorphonuclear Leukocytes*	*Squamous Metaplasia*	*Chronic Inflammatory Cells*	*Ulceration*
Portex tube						
1	1		+			
2	2		+	+		
3	3		+ +	+	+	
4	4		+ +	+	+	+
Vygon tube						
5	1		+			
6	2		+	+		
7	3		+ +		+	
8	4		+ +	+	+	

+ — present, + + — many present.

MATERIALS

The stents used were 1-cm lengths of straight neonatal endotracheal tubes. A 3.0-mm–inside diameter "blue line" Portex tube and a 3.5-mm–inside diameter Vygon tube were compared, as both had an identical outside diameter that fitted snugly into the subglottis. Each tube was cut just prior to its insertion from an unused sterile tube. Twenty-two New Zealand white rabbits 15 weeks of age were used for the study.

METHOD

Intramuscular anesthesia alone was used (Rompun [Burns Veterinary Supply Midwest, Glenview, Ill] 5 mg/kg and Ketaset [Butler Co, Columbus, Ohio] 40 mg/kg), thus avoiding the need for intubation.

A midline incision was made to expose the larynx. The trachea was incised in the midline, and a 1-cm length of stent was introduced in a retrograde manner into the subglottis to lie just beneath the vocal cords (Fig 1A). This was then secured in position with two nylon sutures (Fig 1B). The tracheal incision was then closed, and any potential air leaks were closed with small tags of muscle. The strap muscles and skin were then closed without drainage.

No antibiotics were employed, and infection was not encountered. During the first 24 hours there was a tendency to retain secretions at the laryngeal level, but stridor was not apparent. In one group, animals were killed painlessly at 1, 2, 3, and 4 weeks, while in a second group the stent was removed at 1, 2, 3, and 4 weeks, but the larynx was then closed and the animals were then killed 1 week later. The second group, in which the animal was killed a week after the stent was removed, is called the "delayed" group.

The larynx and trachea were divided transversely into two or three slices that were processed into paraffin histologic blocks and then cut into slides that were stained routinely with hematoxylin and eosin. Most blocks were cut at various levels through their substance. The presence and degree of inflammation were assessed and tabulated.

RESULTS

Tables 1 and 2 show a simplified analysis of the histologic abnormalities seen in the tracheas of ani-

TABLE 2. HISTOLOGIC ABNORMALITIES IN SUBGLOTTIS OF ANIMALS KILLED 1 WEEK AFTER STENT REMOVAL

Animal	*Time Stent Was in Larynx (wk)*	*Normal Tissue*	*Polymorphonuclear Leukocytes*	*Squamous Metaplasia*	*Chronic Inflammatory Cells*	*Ulceration*
Portex tube						
9	1		+			
10	1			+		
11	2		+ +			
12	2	+				
13	3	+				
14	3	+				
15	4	+				
Vygon tube						
16	1		+	+		
17	1	+				
18	2		+			
19	2			+	+	
20	3		+			
21	3		+			
22	4		+		+	

+ — present, + + — many present.

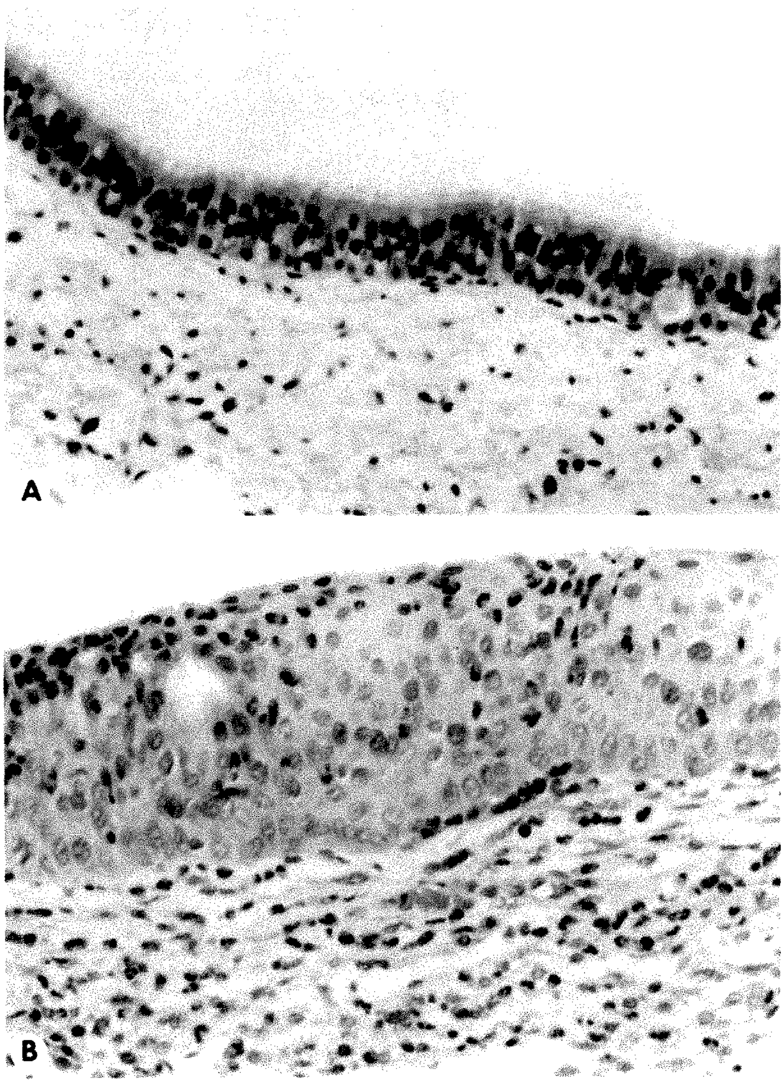

Fig 2. Rabbit subglottic mucosa. A) Normal mucosa from control animal. B) Squamous metaplasia in animal intubated for over 1 week.

mals with a Portex stent and with a Vygon stent. Changes that were obviously due to direct operative trauma, such as suture granulomas, were ignored. Normal mucosa from a control animal is shown in Fig 2A.

In summary, the earliest histologic change seen was polymorphonuclear leukocyte infiltration of the epithelium, with later increasing numbers in the stroma of the mucosa. After only a week's stenting, squamous metaplasia of the respiratory epithelium occurred in a number of animals (Fig 2B).

Infiltration by lymphocytes and plasma cells occurred after 2 to 3 weeks. A superficial ulcer occurred in only one animal, stented for 4 weeks.

In general, the inflammatory response was diminishing in those animals in which killing was delayed by 1 week.

All of the changes seen were limited to the mucosa, with no evidence of damage to the underlying laryngeal skeleton, although clearly ulceration could have progressed.

DISCUSSION

In discussing the etiology of subglottic stenosis, most authors include tube movement as a probable factor. By suturing the stent into the subglottis, we assessed the direct effect of a tube on the tracheal mucosa with movement minimized.

Movement, however, may not be the only factor that is needed to produce stenosis. Supance et al[11] produced stenosis in dogs by suturing a similar length of endotracheal tube into the subglottis, although in their experiment the stent was positioned with the upper end above rather than below the vocal cords. In our experiment the larynx remained competent, while in that of Supance et al,[11] aspiration was a problem. This adds weight to the work of Little et al,[12] who clearly demonstrated that gastric acid can cause otherwise reversible mucosal abnormalities to progress to stenosis.

The acceptance by the larynx of an indwelling stent is encouraging, considering their widespread use in laryngeal reconstruction, although it seems that the stent should not allow refluxed gastric acid to contact the subglottis. The type of stent (hard or soft) does not seem to be important. This accords with our clinical impression, as different centers[1] using different stents still report comparable results.

As intimated at the beginning of this paper, stents may have a place in preventing early immature subglottic stenosis from late scar tissue contracture. Further studies will now be undertaken using the same technique, in which a stent will be introduced through the vocal cords and into a subglottis denuded of epithelium.

CONCLUSIONS

1. Both Portex and Vygon stents produce a mild inflammatory response when secured in the larynx below the vocal cords.
2. Histologic changes increase in frequency and degree with the length of time that the stent remained.
3. The inflammatory response would seem to be reversible, as judged by the lesser degree of inflammation seen in animals killed 1 week after the stent is removed.

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CERAVITAL VERSUS PLASTIPORE IN TYMPANOPLASTY: A RANDOMIZED PROSPECTIVE TRIAL

CHARLES A. MANGHAM, MD ROGER C. LINDEMAN, MD

SEATTLE, WASHINGTON

The hearing results and extrusion rates for ossicular chain reconstruction using a new material called Ceravital, a bioactive glass ceramic, were compared with those for Plastipore, a porous polyethylene that is our standard for synthetic materials. Our null hypothesis was that the results of the two materials were similar. A Ceravital or a Plastipore prosthesis was randomly assigned to 112 consecutive patients. We had 6-month follow-up on 100 patients and 3-year follow-up on 80 patients. The average air-bone gap at 4,000 Hz was 6 dB less with Plastipore than with Ceravital ($p = .036$). Patients were twice as likely to have an air-bone gap of 15 dB or less with Plastipore than with Ceravital (40% versus 21%; $p = .061$). Two of the 38 patients with Ceravital prostheses had a late hearing-result failure due to resorption of the prosthesis material. The materials had similar extrusion rates. We rejected our null hypothesis. The Plastipore group had better hearing results than did the Ceravital group.

KEY WORDS — ceramics, Ceravital, ossicular chain reconstruction, Plastipore, polyethylene, prosthesis, tympanoplasty.

INTRODUCTION

Over the years, the standard for ossicular chain reconstruction has been the sculpted ossicle (for an example, see the article by Wehrs[1]). This is still the choice when the patient's own ossicle can be used; however, frequently the patient's disease process makes autologous ossicles unsuitable. The requirement to eliminate the risk of transmitted diseases such as acquired immunodeficiency syndrome makes homograft ossicles difficult to acquire in our practice. For this reason, like many other surgeons, we have turned to alloplastic materials for ossicular reconstruction.

Plastipore, the trade name for porous polyethylene introduced in the 1970s, is our standard for alloplastic implant materials against which the performance of newer alloplastic materials may be compared. Plastipore fixes to middle ear structures by tissue growth into the pores of the material. Some of this ingrowth is an inflammatory response that may be responsible for some hearing result failures and prosthesis extrusion.[2] Ceravital, the trade name for a specific glass ceramic, fixes to the middle ear by a chemical reaction between the glass ceramic and bone. The prospect of greater biologic compatibility leading to better hearing results and fewer prosthesis extrusions with Ceravital encouraged us to consider reevaluating our use of Plastipore. The purpose of this randomized prospective study is to compare the hearing results and extrusion rates of Plastipore with the hearing results and extrusion rates of Ceravital. Our null hypothesis is that no difference exists between materials.

When our study began in 1983, there were no published reports comparing results with Plastipore and Ceravital. In 1986, Gersdorff et al[3] reported that there was no significant difference between results for Ceravital and Plastipore partial prostheses, but that the results for Ceravital total prostheses were "unquestionably better" than the results for Plastipore prostheses. We did a cross-tabulation of their hearing results by material (Ceravital or Plastipore) controlled for prosthesis (partial or total) that showed an insignificant difference between Ceravital and Plastipore total prostheses (Gersdorff et al,[3] Table 7; degrees of freedom = 3, $\chi^2 = 4.07$, $p = .255$). A more accurate conclusion is that should their results with total prostheses remain constant with additional subjects, then the differences between prostheses would be significant.

METHODS

Subjects. The Research Advisory Committee of the Virginia Mason Research Center reviewed the research plan and the Institutional Review Board approved the written informed consent before patients were enrolled into the study. On the basis of study design considerations discussed below, we planned on having 120 surgical patients: 80 with a partial prosthesis, needed when the incus is absent and the stapes superstructure is present, and 40 with a total prosthesis, needed when both the incus and stapes superstructure are absent (Table 1). Beginning in April 1984, patients were accrued from our surgical practices. A third surgeon was added in

TABLE 1. ENROLLMENT IN STUDY

Material	*Prosthesis*	*Planned*	*Actual*	*6-Month Follow-up*	*3-Year Follow-up*
Plastipore	Partial	40	40	38	31
	Total	20	16	13	11
Ceravital	Partial	40	40	35	26
	Total	20	16	14	12
Total		120	112	100	80

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the second year of patient accrual. The partial-prosthesis group was filled after 15 months. We terminated enrollment with 112 patients after the total prosthesis group was still unfilled after 24 months. The six patients enrolled by the third surgeon were eliminated because the surgeon requested to withdraw from the study. Six of the remaining 106 patients were eliminated because they failed to return for follow-up. We had 6-month follow-up on the remaining 100 patients and 3-year follow-up on 80 patients. Excluding patients who had revision operations, the average follow-up for the Ceravital group was 36.7 months, and it was 36.5 months for the Plastipore group; thus, the variable of duration of follow-up was equalized.

Most of this report involves the 69 patients who had 80 ossicular prosthesis operations and both 6-month and 3-year follow-up. Four of the 69 had ossicular prostheses in both ears. Seven of the 69 had an ossicular prosthesis replaced at a revision operation during the enrollment period. The 69 patients included 32 males who were an average of 45.5 years of age and 37 females who were an average of 51.1 years of age. There were only two patients younger than 16 years of age; therefore, there should be little bias due to differences between results in children and results in adults.

Study Design. In a sample-size analysis we assumed a worst-case scenario, ie, that preoperative and postoperative hearing results had a correlation coefficient no greater than 0.1. In order to detect a true difference of 10 dB between groups 80% of the time with a risk of falsely detecting this difference no more than 5% of the time, we found that we needed 37 subjects in each group. To detect a 5-dB difference, we would need 151 in each group. Although detecting a 5-dB difference was desirable, it was impractical because we anticipated that we would enroll subjects at a rate of 75 per year and we wanted to finish enrollment in 18 months. In a post hoc analysis, the measured correlation between the preoperative pure-tone average air-bone gap (PTA AB gap) and the 3-year postoperative PTA AB gap was 0.20; hence, our actual sample size requirement was 34 in each group to detect a 10-dB difference between groups.

Patients with partial prostheses have a greater chance of meeting a criterion for success than patients with total prostheses.[4] To equally distribute the prosthesis type, we stratified the subjects into those with a partial prosthesis and those with a total prosthesis prior to randomizing between Ceravital and Plastipore. We assumed that other variables that affect hearing results such as stage of disease, and whether the operation was one-stage, two-stage, or a revision, would be equally distributed between the two materials by the randomization process.[5]

Procedure. The surgeon told the circulating nurse whether he would need a partial or total prosthesis. The nurse then opened the appropriate envelope, labeled partial or total, and told the surgeon whether Ceravital or Plastipore was written on a card inside. The surgeon then used the material directed by the contents of the envelope and used the surgical technique appropriate for the prosthesis material. In general, Ceravital prostheses had bone pâte placed on the lateral surface of the prosthesis platform, and Plastipore prostheses had cartilage — some homograft, some autograft — interposed between the platform of the prosthesis and the undersurface of the eardrum. After the operation, the surgeon filled out a data collection sheet. Data from these sheets were then entered into a data base management package (dBase III, Ashton-Tate, Culver City, Calif) run on a microcomputer (Compaq Deskpro, Compaq Computer Corporation, Houston, Tex) and analyzed with a statistical package (ySTAT, Ming Telecomputing, Inc, Lincoln Center, Mass).

The hearing results were reported as pure-tone averages (PTAs) of the difference between bone conduction thresholds and air conduction thresholds for pure tones of 500, 1,000, and 2,000 Hz. We used bone conduction and air conduction threshold data from the same audiogram, rather than using the best preoperative bone conduction score compared with the postoperative air conduction score as suggested by Sheehy[6] (called residual conduction deficit in Gersdorff et al[3]). Average bone conduction scores improved after operation by 2.3 dB for the 6-month data and 1.0 dB for the 3-year data. In other words, Sheehy's method would have resulted in slightly better hearing results, because Sheehy's method would have us using slightly worse bone conduction scores to subtract from our postoperative air conduction scores.

We considered the possibility that there was a correlation between a patient's air conduction threshold and the air-bone gap after operation. This might occur, for example, if patients with more severe disease had worse air conduction thresholds and their severity of disease limited the benefits of operation and left them with large air-bone gaps. We found no correlation between air conduction threshold and air-bone gap.

We decided not to report word recognition scores. We found that having eight different audiologists giving live-voice tests at intensity levels that differed among preoperative tests and postoperative tests introduced variability for which we could not develop controls.

Some surgeons differentiate between a protrusion of the prosthesis, in which a part of the prosthesis can be seen through a defect in the eardrum, and an extrusion, in which the whole platform of the prosthesis can be seen through a hole in the drum. The rationale is that protrusions may have spontaneous

TABLE 2. HEARING RESULTS AT 3 YEARS EXPRESSED AS PERCENTAGE OF PATIENTS

Postop Air-Bone Gap (dB)	*Partial Ceravital, S1 (n = 20)*	*Partial Ceravital, S2 (n = 6)*	*Partial Ceravital, Subtotal (n = 26)*	*Total Ceravital, S1 (n = 5)*	*Total Ceravital, S2 (n = 7)*	*Total Ceravital, Subtotal (n = 12)*	*Ceravital, Total (n = 38)*
≤5	0	17	4	0	0	0	3
≤10	10	17	12	0	0	0	8
≤15	25	17	23	20	14	17	21*
≤20	65	17	54	20	29	25	45
≤25	65	33	58	20	29	25	47
≤30	85	50	77	40	86	67	74
≤50	100	100	100	100	100	100	100

Postop Air-Bone Gap (dB)	*Partial Plastipore, S1 (n = 22)*	*Partial Plastipore, S2 (n = 9)*	*Partial Plastipore, Subtotal (n = 31)*	*Total Plastipore, S1 (n = 5)*	*Total Plastipore, S2 (n = 6)*	*Total Plastipore, Subtotal (n = 11)*	*Plastipore, Total (n = 42)*
≤5	5	0	3	0	0	0	2
≤10	27	11	23	20	0	9	19
≤15	50	33	45	20	33	27	40*
≤20	64	44	58	20	33	27	50
≤25	82	44	71	40	50	45	64
≤30	91	56	81	80	67	73	79
≤50	100	100	100	100	100	100	100

S1 — surgeon 1, S2 — surgeon 2.

*Difference between Ceravital and Plastipore for ≤15 dB, $\chi^2 = 3.50$, $p = .061$.

eardrum healing, whereas extrusions do not heal. We labeled both protrusions and extrusions as "extrusions" if there was any prosthesis showing at any time during the 3-year follow-up. This resulted in an overestimate of extrusion rate by about 20%, since some of the protrusions have since healed.

To determine if differences in technique could account for the difference in surgeons' results, we had to identify the surgeons. In order to make the reader unaware of which surgeon used which technique, we have randomly assigned one of the surgeons the code name "surgeon 1," and the other the name "surgeon 2."

RESULTS

Differences Due to Material and Type of Prosthesis. The 3-year hearing results are shown in Table 2. The first column shows seven outcomes for differences between air conduction and bone conduction PTA scores ranging from 5 dB or less to 50 dB or less. The second column shows the results for surgeon 1 using partial prostheses. In column 2, data rows 1 through 7 show the results with use of partial Ceravital prostheses, and data rows 8 through 14 show the results of partial Plastipore prostheses. The third column shows the results for surgeon 2 using partial prostheses. The fourth column has the average hearing results with partial prostheses for surgeon 1 and surgeon 2 obtained by averaging the results in columns 2 and 3. The fifth column shows the results for surgeon 1 using total Ceravital prostheses and total Plastipore prostheses. The sixth column shows the results for surgeon 2 using total prostheses. The seventh column has the average hearing results with total prostheses for surgeon 1 and surgeon 2, obtained by averaging the results in columns 5 and 6. The eighth column, an average for partial and total prostheses, is the average of columns 4 and 7.

There was a trend toward better hearing results with Plastipore than with Ceravital. The greatest difference between materials occurred when an air-bone gap of 15 dB or less was considered the criterion for success. In column 8, 21% (8 of 38) of results with a Ceravital prosthesis were successful, compared with 40% (17 of 42) of results successful with Plastipore ($\chi^2 = 3.50$, $p = .061$). There were no "dead ears," ie, ears with no hearing at the limits of the audiometric output.

Table 3 shows the air-bone gaps at 3 years as a function of stimulus frequency. Both groups had a similar pattern of result, with the smallest mean air-bone gap occurring at 2,000 Hz. At 4,000 Hz, the Plastipore group had a mean hearing level that was 6.04 dB better than the Ceravital group (26.07 dB HL versus 32.11 dB HL; ANOVA, F-statistic = 4.39, $p = .036$).

Surgeon 1 experienced 13 of the 14 extrusions. The extrusions were similarly distributed between the materials, Ceravital and Plastipore, and between the prosthesis types, partial and total.

TABLE 3. AIR-BONE PURE-TONE AVERAGE (dB) AT 3-YEAR FOLLOW-UP

		Frequency (Hz)				
Material		*250*	*500*	*1,000*	*2,000*	*4,000**
Ceravital (n = 38)	Mean	37.37	27.89	30.66	16.84	32.11
	SD	19.20	16.05	15.65	15.70	14.69
Plastipore (n = 42)	Mean	33.81	25.24	27.74	16.43	26.07
	SD	17.59	17.11	15.19	15.03	10.96

*ANOVA for differences between materials at 4,000 Hz: F-statistic = 4.39, $p = .036$.

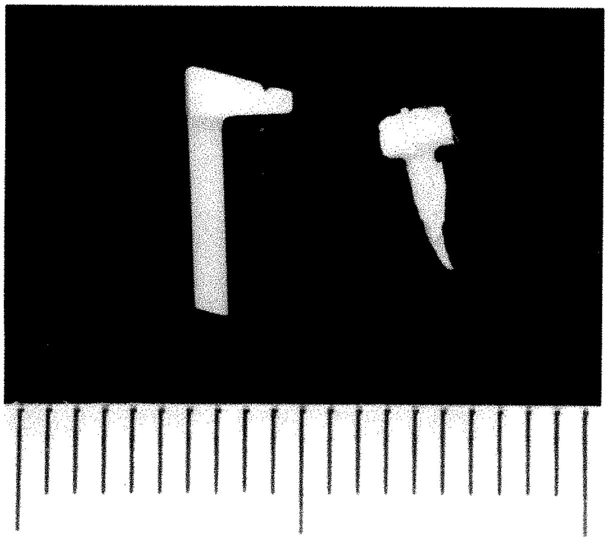

Fig 1. Ceravital total prosthesis as received from manufacturer is shown on left. Total prosthesis removed from middle ear of 18-year-old girl 3 years after original operation is shown on right. Rule is in millimeters.

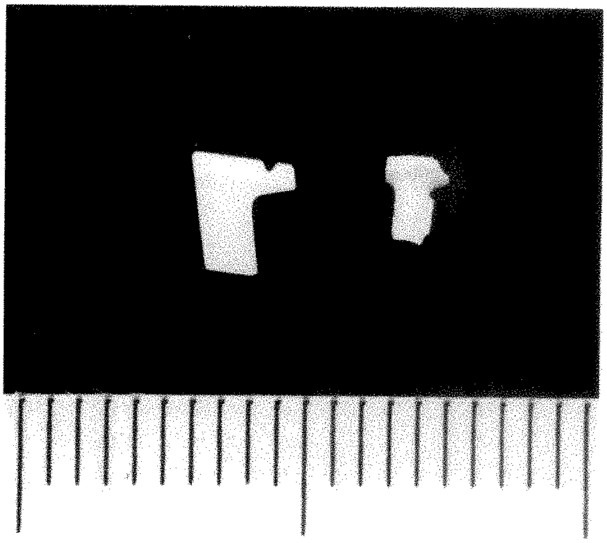

Fig 2. Ceravital partial prosthesis as received from manufacturer is shown on left. Partial prosthesis removed from middle ear of 72-year-old woman 3 years after original operation is shown on right. Rule is in millimeters.

Differences Due to Surgical Technique. As shown in Table 2, surgeon 1 had better hearing results than surgeon 2, an unexpected finding. In an exploratory analysis, we found that surgeon 1 had hearing results that were 15 dB better than the hearing results for surgeon 2 in the case of one-stage ossicular chain reconstructions (surgeon 1, mean = 19.00 dB; surgeon 2, mean = 34.39 dB; ANOVA, F-statistic = 4.53, p = .025). Further, surgeon 1 did all 29 of the second-stage reconstructions, with surgeon 2 electing to revise the one-stage cases that were failures from a hearing point of view rather than do a planned second stage. Other differences between surgeons were secondary to the effect of staging operations.

We performed exploratory analyses on all hearing-result differences greater than 5 dB. There were six such analyses; therefore, we had about a 30% probability of finding that one of these analyses would have a p value of .05 or less by chance.

DISCUSSION

We rejected the null hypothesis that differences between Ceravital and Plastipore were insignificant, on the basis of our finding that the Plastipore group was twice as likely as the Ceravital group to have a postoperative air-bone gap of 15 dB or less. Further, the Plastipore group had a 6-dB smaller air-bone gap at 4,000 Hz than the Ceravital group.

Our results with Plastipore were comparable to those achieved by Gersdorff et al[3]; however, our results with Ceravital were not as good as the results of the Gersdorff group. One explanation for our poorer results with Ceravital is that we had several years' prior experience with Plastipore, including one author's having fellowship training with a group with extensive experience with Plastipore. By contrast, neither of us began using Ceravital before preparing for this study. There may be technical factors that are required for success with Ceravital that cannot be gained from talking to the manufacturer's representatives or from experience in the laboratory. A surgeon starting to use Ceravital should consider getting training from an individual or group with good results from this prosthesis.

A factor that may lead to long-term failure with Ceravital prostheses is the variable rate of prosthesis absorption. In animal studies, areas of lysis of the prosthesis material occur that are as deep as 250 μm at 1 year and as deep as 450 μm after 2 years.[7] We had two patients who had a progression in hearing loss at about 3 years related to resorption of the prosthesis in the area in which the prosthesis was making contact with the sound-conducting mechanism (Figs 1 and 2).

An unexpected finding was a difference between the hearing results and extrusion rates of surgeon 1 and surgeon 2. Our explanations were related to staging the operation and the length of the prosthesis (the operation was staged according to guidelines described by Sheehy[6] and Sheehy and Crabtree[8]). Had we known about the confounding effect of differences in staging, we would have controlled for this variable by having the surgeons use the same indications for staging.

Our other unexpected finding, the high extrusion rate for surgeon 1, was probably related to prosthesis length. Our speculation was that surgeon 1 tended to use a longer prosthesis than surgeon 2. A longer prosthesis would be less likely to lateralize from the stapes footplate or stapes capitulum and less likely to medialize from the eardrum or malleus. The longer prosthesis would be more likely to extrude through the eardrum, so there is a penalty with these materials for using a long prosthesis.

Sharp corners predisposed a prosthesis to extrusion. When the platform of a Plastipore prosthesis was cut into a T shape, similar to the Fisch design, the prosthesis tended to extrude at the corners. The Ceravital prosthesis tended to extrude at a corner or at one of the edges of the groove cut in the lateral surface of the platform for the malleus handle.

Results in this study should be compared with caution to results of other studies because of confounding variables such as differences in patient self-selection for follow-up. In this study, for example, the nine patients with Plastipore prostheses who returned for 6-month hearing tests but did not return for 3-year hearing tests had a better average hearing result at 6 months by 5.9 dB than their 42-patient cohort that did not drop out of the study. The 11 patients with Ceravital prostheses who dropped out had a better average hearing result at 6 months by 1.4 dB than their 38-patient cohort that did not drop out. This suggests that our 3-year data underestimate the hearing results achieved with these two prostheses. Further, the 3-year data tend to underestimate the difference between the Plastipore and the Ceravital group.

Another cause of differences among published results would be the bias introduced by the surgeon. In this study, the decision to use Ceravital or Plastipore was made by a random assignment of prosthesis material. By contrast, Niparko et al[9] used a nonrandom assignment of prosthesis material: "Ceravital...was used when an incus autograft was not obtainable or not suitable for reconstruction." Other possible causes of bias include the staging of the operation and whether the malleus was present or absent, as described above, as well as the severity of disease.[5]

SUMMARY

The hearing results with Plastipore were better than the results with Ceravital. Technical factors such as staging the operation in cases of mucosal loss, the height of the prosthesis, and the shape of the prosthesis platform were as important in determining the final hearing result and extrusion rate as was the material used.

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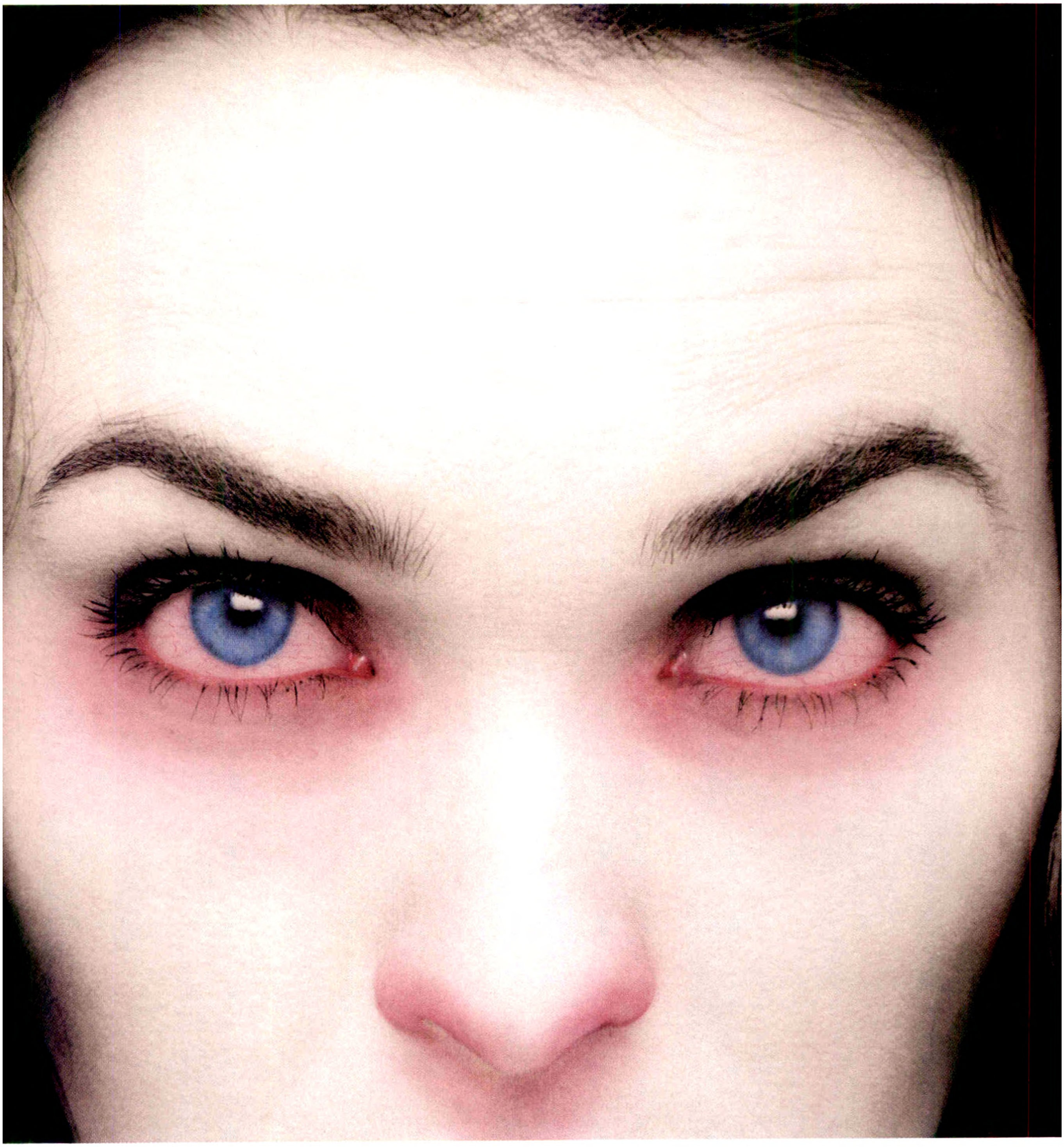

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AURAL IRRIGATION WITH WATER: A POTENTIAL PATHOGENIC MECHANISM FOR INDUCING MALIGNANT EXTERNAL OTITIS?

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We hypothesized that the forcible introduction of water containing *Pseudomonas aeruginosa* into the ear canal of a susceptible host (an elderly diabetic with cutaneous hypoperfusion secondary to microangiopathy) was the inciting factor in the development of malignant external otitis. Tap water irrigation of the ears by a physician preceded the onset of symptoms in 61.5% (8/13) of cases of malignant external otitis. Two control subjects with known diabetes mellitus were matched for each patient by sex and age. Both groups were questioned on the nature and degree of aural water exposure, as well as history of ear disease. There were no significant differences between 13 patients and 26 control subjects for presence of ear disease (hearing loss, chronic infection, prior operations), swimming, showering, bathing, frequency of ear cleaning, or method of ear cleaning (washcloth, cotton applicator). Patients with malignant external otitis had a statistically significant higher incidence of aural irrigation with tap water when compared with control subjects. We suggest that a substantial number of cases of malignant external otitis may be iatrogenic.

KEY WORDS — iatrogenic disease, malignant external otitis, necrotizing external otitis, *Pseudomonas aeruginosa*.

INTRODUCTION

Malignant external otitis is an invasive bacterial infection of the external auditory canal with high morbidity and a 20% mortality rate despite appropriate antibiotic therapy.[1] The pathogenesis of this infection is unknown. Pertinent, and as yet unexplained, variables include the selective predilection for elderly patients with diabetes mellitus and the near-universal recovery of *Pseudomonas aeruginosa* from the ear canal. Intrigued by the history of coincidental occurrence of ear irrigation with water in two patients within a week prior to the onset of their symptoms of malignant external otitis, we conducted a case-control study to assess the degree and nature of aural water exposure in patients at risk for the development of this severe infection.

METHODS

There were 13 cases of malignant external otitis. *Pseudomonas aeruginosa* was recovered from the ear canal in all patients. The control subjects were 26 persons with diabetes mellitus who were selected from a population of known diabetic patients on file at the Pittsburgh Diabetes Center, University of Pittsburgh. Two control subjects for each case were selected by matching for sex and age (±5 years).

In both groups, a questionnaire was administered requesting information on the nature and degree of aural water exposure, as well as any history of ear disease. Variables assessed included swimming, bathing, and showering frequency, in addition to any history of aural irrigation. Otologic history included hearing loss, infections, presence of cerumen, and prior operations.

Data were interpreted by matched pair analysis. A Mantel-Haenszel estimate of the odds ratios was calculated from the frequencies of each triplet outcome. The Mantel-Haenszel X^2 was used to assess the significance of the odds ratio.[2]

RESULTS

Patients. There were four women and nine men. Their ages ranged from 48 to 92 years, with a mean of 73 years. Eleven patients exhibited some degree of glucose intolerance. Seven patients were insulin-dependent, two patients used an oral hypoglycemic agent, and two had abnormal glucose tolerance test results.

Control Subjects. The control subjects consisted of 8 women and 18 men with a mean age of 69 years (range, 44 to 93). Thirteen were insulin-dependent, 12 took an oral hypoglycemic, and 1 had diabetes that was controlled with diet alone.

Eight (61.5%) of the patients had a history of aural irrigation, usually within 2 weeks prior to the onset of symptoms attributed to malignant external otitis. In contrast, only 15.4% (4/26) of control subjects displayed any history of ear water exposure (see Table).

With respect to ear disease, no control subjects had malignant external otitis, one had a history of "ear infections" (unspecified), and five admitted to a documented hearing loss, although only one used amplification. The majority of those in both groups admitted to routine ear cleaning: 91.7% (11/12) versus 96.2% (25/26) (see Table). Three of 12 (25%) patients with malignant otitis went swimming on a regular basis (once a week or more), as did 19.2% (5/26) of control subjects. Showering was the favorite method of cleaning in 100%

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CHARACTERISTICS OF PATIENTS AND CONTROL SUBJECTS

	Patients With Malignant External Otitis	*Control Subjects*
Mean age (range)	73 (48-92)	69 (44-93)
Male	69.2% (9/13)	69.2% (18/26)
Female	30.8% (4/13)	30.8% (8/26)
Diabetes mellitus		
Insulin-dependent	53.8% (7/13)	50.0% (13/26)
Oral agents	15.4% (2/13)	46.2% (12/26)
Diet alone	15.4% (2/13)	3.8% (1/26)
Ear disease*	100.0% (13/13)	23.1% (6/26)
Potential water exposures†		
Aural irrigation§	61.5% (8/13)	15.4% (4/26)
Swimming	25.0% (3/12)	19.2% (5/26)
Showering	100.0% (12/12)	96.2% (25/26)
Bathing	41.7% (5/12)	46.2% (12/26)
Ear cleaning (any)‡	91.7% (11/12)	96.2% (25/26)
Q-tip	33.3% (4/12)	38.5% (10/26)
Washcloth	66.7% (8/12)	61.5% (16/26)

*Defined as history of chronic infection, hearing loss, or prior operation.

†One patient died prior to study, before questionnaire could be administered.

§p<.05, matched pair analysis.

‡One patient used both cotton applicator (Q-tip) and washcloth for cleaning.

(12/12) of the patients with malignant otitis and in 96.2% (25/26) of control subjects. Only the difference in prior aural irrigation between the two groups was statistically significant (p<.05).

DISCUSSION

Pseudomonas aeruginosa is a gram-negative bacterium that, as a ubiquitous saprophyte, is widely distributed in soil, water, sewage, and plants.[3] The organism is also capable of proliferating in distilled water.[4] Prospective surveys in diabetic patients have shown that *P aeruginosa* is *not* a component of normal flora in the external ear canal.[5,6] In fact, there appears to be no difference in the ear canal flora of diabetics and that of normal hosts.[7]

Contamination of water by *Pseudomonas* has been associated with the development of clinically significant infections in the immunocompetent host. External otitis, in fact, has been coincident with the presence of *P aeruginosa* in inadequately chlorinated whirlpools.[8] *Pseudomonas aeruginosa* has also been isolated from the ear canals of patients with simple external otitis that was similar in serotype and phage type to *Pseudomonas* isolated from a recreational water site in which the subjects had recently been swimming.[9] In one prospective study, the degree of water exposure in the ear canal was directly correlated with the incidence of external otitis.[5]

This study demonstrated a significantly higher incidence of aural irrigation in patients with malignant external otitis compared to elderly diabetics matched for age and sex but without evidence of this invasive *Pseudomonas* infection. If the combination of diabetes and advanced age was a sufficient predisposing factor for the development of malignant external otitis, one would anticipate no difference in aural water exposure between these two groups.

Forceful introduction of water can traumatize the external canal. We propose that the diminished cutaneous perfusion characteristic of elderly patients with diabetes mellitus could enable *P. aeruginosa* to establish a foothold from which it might then advance insidiously into the adjacent temporal bone. The trauma induced by aural irrigation may be important. One patient vividly recalled the acute onset of severe pain with forcible irrigation.

The temporal relationship between the instillation of water into the ear canal (which may contain *P aeruginosa*) and the acute onset of the symptoms of malignant external otitis is consistent with our proposed pathogenic mechanism. Patients with malignant external otitis typically experience severe otalgia of acute onset,[1] while patients with chronic suppurative otitis media have minimal otalgia. The latter infection typically occurs over a number of years in patients with a history of preexisting ear disease and also involves *P aeruginosa*.[10] Finally, it is noteworthy that prior aural irrigation has been noted in other case reports of malignant external otitis.[11-17]

These are obvious weaknesses in our study. Although we identified two control subjects for each experimental subject, the sample size remains small. This is primarily explained by the rarity of malignant external otitis (fewer than 300 cases reported in the world literature).[1] In any retrospective study, there is always the possibility of undetected bias in eliciting a positive response; however, by asking for other information (eg, history of ear disease, methods and timing of ear cleaning, and swimming, shower, and bath frequency), the patient's attention was distracted from the specific topic of aural irrigation.

In summary, the pathogenesis of malignant external otitis is unknown. We propose the following scenario. Elderly patients with diabetes mellitus, the high-risk group for acquiring this infection, have a diminished cutaneous barrier against infection because of microangiopathy associated with diabetes. Aural irrigation with tap water may be an initiating factor for two reasons: 1) forcible irrigation can traumatize the skin of the external ear canal, and 2) the tap water may be colonized with *P aeruginosa*. Once the organism is introduced, superficial infection is established. It should be noted that *P aeruginosa* is also the most common cause of simple external otitis. In an elderly diabetic patient, the organism may penetrate the cutaneous barrier and progress into cartilage and bone and become established as a deep-seated infection. The complex combination of variables (diabetes mellitus, advancing age, trauma to the ear canal, introduction of *P aeruginosa*) also explains the rarity of this condition.

Thus, we point out that a significant proportion of cases of malignant external otitis could be iatrogenic, in that the precipitating event occurs in the physician's office. The otolaryngologist, as well as the primary-care physician, should avoid aural irrigation in the elderly patient with diabetes mellitus. If aural irrigation is required in the high-risk patient, we recommend that sterile water be employed. This clinically relevant hypothesis requires confirmation by other physicians.

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FACTORS INFLUENCING THE PROBABILITY OF RESIDUAL CHOLESTEATOMA

RONALD E. GRISTWOOD, CHM, FRCS(EDIN), FRACS   WILLIAM N. VENABLES, BSC, PHD

ADELAIDE, AUSTRALIA

Data from the records of 251 consecutive patients with aural cholesteatoma treated surgically by one surgeon (R.E.G.) between 1962 and 1980, using mainly wide access approaches of atticotomy and attico-antrostomy, and assiduously followed up, formed the basis of an analysis to determine what variables influence the chance of residual cholesteatoma. There were 42 cases of residual cholesteatoma: 20 in the mesotympanum (including two annular), 17 in the epitympanum, and five in the mastoid. The most important variables for the prognosis of residual disease included age, the state of the stapes, the state of the middle ear mucosa, and the number of sites in the middle ear cleft affected by cholesteatoma. A logistic model was constructed to describe the dependence of the probability of residual cholesteatoma on the two determining variables age and state of the stapes. The implications of these findings for the surgical management of cholesteatoma are discussed.

KEY WORDS — attico-antrostomy, atticotomy, logistic modelling, modified radical mastoidectomy, residual cholesteatoma.

INTRODUCTION

Residual cholesteatoma refers to one that develops from residual fragments of living matrix inadvertently retained within the middle ear cleft at the original operation. Continued growth of the remnant forms a circumscribed, slowly expanding, keratin-containing cyst resembling a pearl. Such a condition developing after middle ear and mastoid surgery is an important clinical complication of the surgical management of cholesteatoma.

The difficulties in assessing the real incidence of residual disease have been described previously.[1] Analysis has shown that some variables have a marked influence on the probability of residual disease, while others could not be established as significant.

MATERIALS

The data from the records of 251 consecutive cases of cholesteatoma, treated surgically by the same surgeon (R.E.G.) between the years 1962 and 1980, using mainly the wide access approaches of atticotomy and attico-antrostomy, and assiduously followed up, formed the basis of the analysis. Forty-two cases of residual cholesteatoma were discovered: 20 in the mesotympanum (including two annular), 17 in the epitympanum, and five in the mastoid.

METHODS

Whether or not an incidence of residual disease is discovered depends largely on the period of follow-up for the patient. The analysis, accordingly, is restricted to those patients who have shown residual cholesteatoma (n = 42) or who have had at least 60 months of follow-up free of disease (n = 142). The χ^2 test has been used as a screening device to determine those variables that appear to be important in the prognosis of residual disease. Log-likelihood ratio statistics have been used in preference to the classical Pearson statistic.[2] Finally, a model was developed to estimate the probability of residual disease as a function of the important determining variables. A standard logistic model was used for this purpose.[3]

FOLLOW-UP STUDY

The potential and actual numbers of cases followed up are shown in Fig 1, while the actual num-

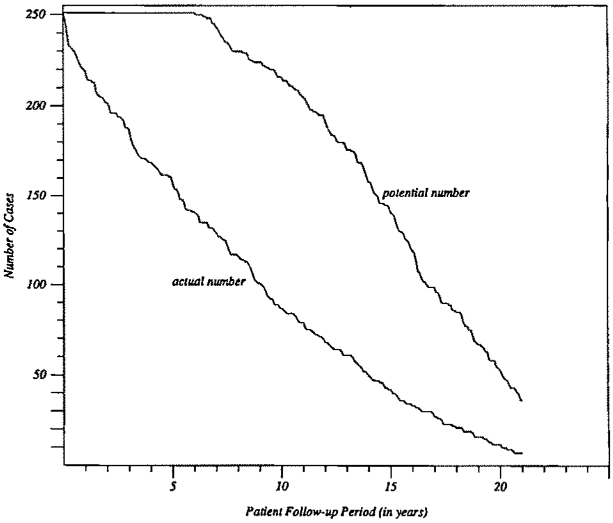

Fig 1. Potential and actual numbers of cases with follow-up time equaling or exceeding specified period.

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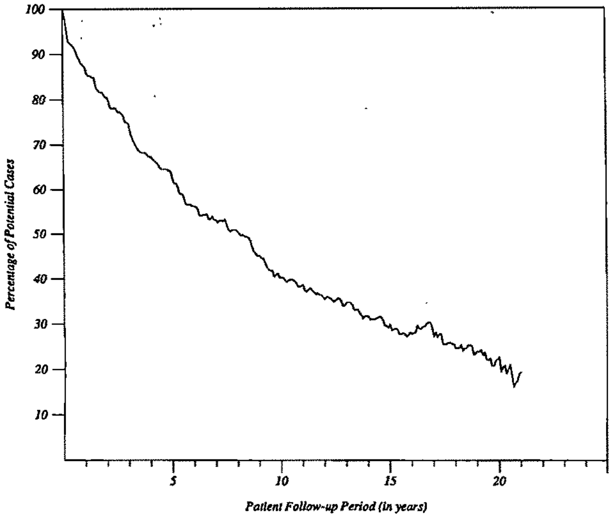

Fig 2. Actual number of cases with specified minimum follow-up time as percentage of potential number of cases.

ber of cases as a percentage of the potential number of cases is shown in Fig 2. For example, of the 251 cases, 157 (or 62.6%) were followed up for at least 5 years, and 141 (or 56.2%) were followed up for at least 6 years postoperatively. At 10 years, 87 cases out of a potential 216 (or 40.3%) and, at 15 years, 42 out of a potential 141 cases (29.8%) had been followed up.

Long-term studies are always difficult to achieve. Patients may be unable or unwilling to return for review for many reasons, including forgetfulness, disinterest, inconvenience, expense, distance, change of residence, old age, infirmity, or death. Such studies are time-consuming, and they require motivation on the part of both doctor and patient. It is a universal experience that the number of patients who attend for review falls off progressively with time.

RESULTS

The results of the χ^2 tests show that the most important variables for the prognosis of residual disease include 1) age (p = .003), 2) the state of the stapes (p = .005), 3) the state of the middle ear mucosa (p = .01), and 4) the number of sites in the middle ear cleft affected by cholesteatoma (p = .06).

The age of the patient and the state of the stapes appear to make nearly independent contributions, but other variables established as important, namely the state of the middle ear mucosa and the number of sites affected, appear to owe their apparent influence to a strong association with age.

Age. Age at operation has a strong effect on the probability of residual disease, with young patients more at risk than the older patient (p = .003). The proportion of cases of residual disease decreases dramatically with the age of the patient, as is evident from Table 1. Figure 3 illustrates the cumulative percentage of cases that result in residual cholesteatoma after surgery. Of the three coarse age groupings, that of the ages up to 20 has the steepest increase and the greatest incidence, reaching 32% after 8 years, while the older age groupings reach only about 11% in the same time. After 8 years, discovery of residual disease almost ceases in all age groups. The period of the first 4 years after surgery sees the most rapid increase in discovery of residual disease, followed by a period of slow increase to about 8 years.

TABLE 1. AGE AT OPERATION VERSUS RESIDUAL DISEASE

Age (yr)	*No Residual Disease and at Least 5 Years' Follow-up*	*Residual Cholesteatoma*	*Total*
17 or younger	15	17	32
18-30	28	7	35
31-40	27	9	36
41-55	34	6	40
56 or older	19	3	22
Total	123	42	165

Highly significant ($\chi^2 = 16.11$, df = 4, p = .003).

State of Stapes. The condition of the stapes appears to be important as a prognostic indicator of residual disease. Those cases in which the stapes is covered by cholesteatoma matrix or in which the crura of the stapes have been destroyed by disease involve a greater risk than those in which the stapes is normal or intact and fixed (Table 2).

State of Middle Ear Mucosa. Those cases in which the middle ear mucosa is replaced by matrix, or in which the mucosa has become polypoidal, have (not unexpectedly) a greater chance of residual disease than cases in which the mucosa is normal, hypertrophic, or tympanosclerotic, or in which it shows adhesions (Table 3).

Number of Sites Affected by Cholesteatoma. Cases were classified as to whether cholesteatoma

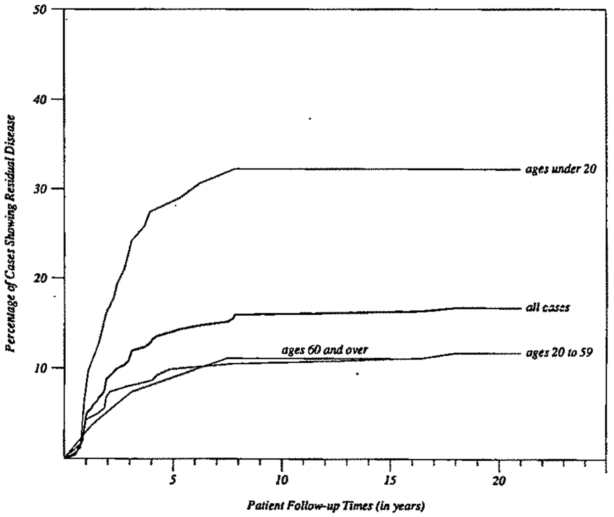

Fig 3. Cumulative percentage of cases showing residual disease after operation for cholesteatoma.

TABLE 2. STATE OF STAPES VERSUS RESIDUAL DISEASE

State of Stapes	*No Residual Disease and at Least 5 Years' Follow-up*	*Residual Cholesteatoma*	*Total*
Normal or intact with footplate fixation	79	15	94
Covered by matrix	8	6	14
Crura absent	36	21	57
Total	123	42	165

Highly significant ($\chi^2 = 10.53$, df = 2, $p = .005$).

involved one or more of the following sites — mastoid, attic, mesotympanum, or protympanum. Analysis showed the effect to be marginally significant, those cases with three or all four sites involved in the original cholesteatoma showing a tendency to higher rates of residual disease than those with only one or two sites involved (Table 4). This variable appears to owe its significance to a close connection with age.

Other Variables Considered. Other variables that could be considered a priori as potentially influential, such as the type of operation (Table 5), the graft procedure, or the presence of moisture in the middle ear, could not be established as significant in our study.

Model-Based Estimates of Probability of Residual Disease. The logistic model is an adaptable and robust model frequently used to describe the dependence of a probability on one or more determining variables. If $x1$, $x2, \ldots, xk$ are the levels of the determining variables and p is the probability of the event of interest, the model takes the form

$$p = \frac{\exp(\eta)}{1 + \exp(\eta)}$$

where $\eta = \beta 0 + \beta 1x1 + \ldots + \beta kxk$ and $\beta 0, \beta 1, \ldots, \beta k$ are parameters to be estimated from the data.

Standard techniques for screening variables in the construction of such models indicate that only two determining variables need be included in the model in this case, namely "age" and "stapes." Age is a quantitative variable and is included as such, but stapes is qualitative. Patients are classified into two groups for modeling purposes. Group 1 consists of patients with an absent crura and a mobile footplate or cholesteatoma matrix on the stapes, and group 2 consists of patients with a normal or intact and fixed stapes. The simplest way to accommodate the two groups within the model is to allow the parameter $\beta 0$ to vary with the group. Subsequent checks confirm that this is adequate. The estimated parameters are then $\eta = 0.687 - 0.0388$ x age for group 1, and $\eta = -0.354 - 0.0388$ x age for group 2.

TABLE 3. STATE OF MIDDLE EAR MUCOSA VERSUS RESIDUAL DISEASE

State of Middle Ear Mucosa	*No Residual Disease and at Least 5 Years' Follow-up*	*Residual Cholesteatoma*	*Total*
Polypoid change	30	12	42
Cholesteatoma matrix	35	20	55
All others	58	9	67
Total	123	41	164*

Very significant ($\chi^2 = 9.24$, df = 2, $p = .01$).

*One case did not have observation recorded.

TABLE 4. NUMBER OF SITES OF CHOLESTEATOMA VERSUS RESIDUAL DISEASE

*No. of Cholesteatoma Sites**	*No Residual Disease and at Least 5 Years' Follow-up*	*Residual Cholesteatoma*	*Total*
1	30	9	39
2	62	15	77
3	28	13	41
4	3	5	8
Total	123	42	165

Marginally significant ($\chi^2 = 7.32$, df = 3, $p = .06$).

*Mastoid, attic, mesotympanum, or protympanum.

Standard errors for the estimates are shown in parentheses as follows. For group 1, $\beta 0 = 0.687$ (0.44) and $\beta 1 = 0.0388$ (0.012). For group 2, $\beta 0 = -0.354$ (0.47) and $\beta 1 = -0.0388$ (0.012).

Probabilities calculated from the estimated model are shown in Fig 4 as two separate curves giving probability as a function of age for each group.

Since the other variables established as important for the prognosis of residual disease appear to owe their influence to a strong association with age, their inclusion in addition to age does not seem to contribute any further predictive capacity to the model, and hence they are omitted. Standard statistical screening techniques confirm this point.

It could be argued that excluding from the study those patients without disease but with less than 60 months' follow-up has biased the estimation of the model, since most of these patients, particularly those with at least, say, 36 months' follow-up will

TABLE 5. TYPE OF OPERATION VERSUS RESIDUAL DISEASE

Type of Operation	*No Residual Disease and at Least 5 Years' Follow-up*	*Residual Cholesteatoma*	*Total*
Transcanal intact canal wall	10	4	14
Intact canal wall and mastoidectomy	4	3	7
Extended atticotomy	38	8	46
Attico-antrostomy	62	24	86
Attico-antrostomy and mastoid obliteration	9	3	12
Total	123	42	165

Nonsignificant ($\chi^2 = 3.05$, df = 4, $p = .55$).

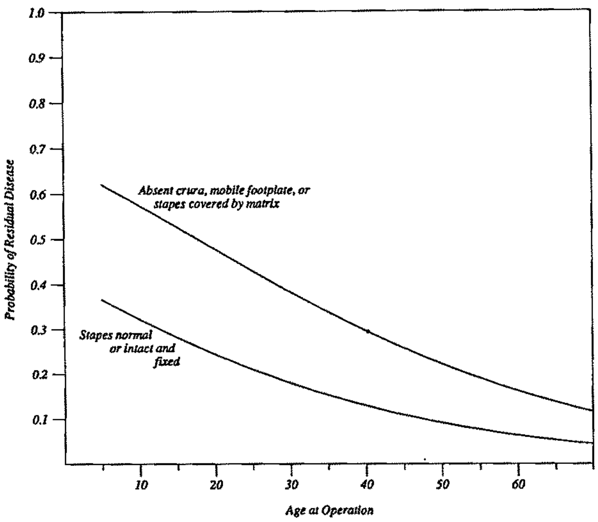

Fig 4. Estimated probability of residual disease as function of age and state of stapes.

be in fact free of disease. This is a matter of judgment, since the number of patients with very inadequate follow-up who in fact do have the disease is also unknown. However, if follow-up time is ignored completely and all patients are included, there clearly will be a bias in the other direction. If the model is so fitted, however, the estimates are reduced, but not greatly, and the main qualitative features of the estimates are preserved.

DISCUSSION

This study has confirmed that younger patients do appear to have the most serious forms of cholesteatoma, with a greatly increased risk of residual disease. This increased risk in the younger patient may be due to one of the following.

1. The infiltrating nature of matrix in cases of diffuse cholesteatosis of a pneumatized mastoid increasing the difficulty of removal and increasing the chance of leaving in situ a fragment of viable squamous epithelium.
2. Residues of matrix in the child possibly having a greater potential for survival and growth than similar remnants in the elderly.
3. The more frequent occurrence of complicated patterns of involvement of the middle ear cleft by cholesteatoma in younger patients.

The increased probability of residual disease in the younger person has reaffirmed the surgical author's (R.E.G.) opinion that open approaches are greatly to be preferred to closed techniques in the surgical treatment of cholesteatoma in childhood, even in the presence of a pneumatized mastoid. Attico-antrostomy, with removal of the outer walls of the attic and mastoid together with the bony posterior canal wall as far medially as the fallopian canal, permits the widest possible access for removal of extensive disease and can be accompanied in the same procedure by repair of tympanic membrane defects by use of underlay grafting techniques. In this way a sealed and aerated mesotympanum usually will develop. The general advantages of such wide-access approaches include improved exposure of the attic in the small sclerosed mastoid with low-lying middle fossa dura and a forward-placed sigmoid sinus. Removal of disease is easier and more certain than with intact canal wall techniques, and this can only diminish the chance of residual disease. Residual epidermoid cysts developing in the attic and mastoid usually can be detected easily and early, and many can be removed by a simple office procedure. Furthermore, this technique avoids the formation of retraction pocket cholesteatoma — the so-called "recurrent" cholesteatoma — seen after intact canal wall procedures.

In the younger person, attico-antrostomy in the pneumatized mastoid is followed not infrequently by considerable contracture of the cavity, with sound healing and spontaneous epithelialization within 4 to 6 weeks.

The increased incidence of residual disease within the middle ear of patients who have matrix enveloping an intact stapes or who have destruction of the crural arch by disease is explained by the technical difficulty of removing completely and with certainty the cholesteatoma matrix from the internal aspect of an intact crural arch or from a deeply placed sinus tympani.

It would seem wiser in patients who have cholesteatoma matrix lining the nooks and crannies of the mesotympanum, or who have polypoidal mucosa, to delay any ossicular reconstruction to a later date determined by freedom from residual disease after adequate follow-up.

It is clear that many cases of residual disease will be missed unless there are adequate follow-up studies.

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SURGICAL TREATMENT FOR LARYNGEAL PARALYSIS IN INFANTS AND CHILDREN

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Clinical and endoscopic data of 219 cases of laryngeal paralysis in newborns, infants, and children are briefly reported. The management of severe cases of persistent dyspnea then is discussed, according to the literature. Of 219 cases, 22 young patients underwent a surgical procedure because of lack of spontaneous recovery and poor tolerance of their disease after 6 to 9 months of follow-up. Arytenoidectomy technique has been used three times and arytenoidopexy 19 times, with fair to excellent results. Other possible treatments for infants are discussed. On the basis of this important series of surgical pediatric cases, the arytenoidopexy technique is advocated, besides arytenoidectomy, to avoid the risks of a long-term tracheostomy in young patients with vocal cord paralysis and severe dyspnea.

KEY WORDS — arytenoidectomy, arytenoidopexy, child, infant, laryngeal paralysis, neonate, tracheotomy.

The natural history of laryngeal paralysis (LP) in newborns, infants, and children certainly depends on its cause. But it is well known that many neonates recover spontaneously within a few weeks after birth.[1-6] Some patients, however, do not recover in the first months and have various degrees of persistent dysphonia, stridor, and dyspnea. This can lead to temporary endotracheal intubation and tracheotomy in cases of respiratory distress, chronic hypoxemia, and failure to thrive.[3-5,7] At this point, controversy exists about further management.

Some authors advocate a waiting attitude: the child grows with a tracheostomy tube in place for about 6 years. Then, if there is no spontaneous recovery, surgery is proposed when the patient is old enough that a choice can be made between a good voice with a fenestrated cannula and a possibly weak voice without a tracheostomy.[3,7] Also, knowing the main aim of this management (to get rid of the tracheostomy tube) and the disadvantages of surgical treatment (risk of a weakened voice), other authors perform surgery much earlier in order to avoid the burden and risks of a long-term tracheostomy in an infant.[5,8] The proposed techniques are numerous: reinnervation with a nerve-muscle flap,[9] arytenoidectomy (anterior,[10] lateral,[11,12] or endoscopic[13] approach), cordopexy,[8] and arytenoidopexy.[14] However, most of the published cases involve adults, and the series of surgical cases in children are still small.[3,5,7,15]

As in cases of laryngeal stenosis[16] or extremely severe laryngomalacia,[17] we have always considered long-term tracheostomy in infants as a high-risk situation, as do some other authors.[18] Hence, we strongly favor surgery. In cases of clinically severe neonatal LP, we have adopted the following strategy. After initial endotracheal intubation, repeated attempts at extubation and flexible laryngoscopy are performed every 2 weeks, in hope of a spontaneous recovery. If this does not occur at 2 or 3 months of age (depending on the infant's weight and tolerance of the endotracheal tube), a tracheotomy is performed. A flexible laryngoscopy and an attempt to plug the tube are performed every month. In our experience, spontaneous recovery occurs in most cases before 4 months of age if it does occur. We know that some authors have reported that recoveries occurred after 5 years[15] and 9 years.[6] But this seems to be too long a delay to decannulate a child. The tracheostomy care represents a heavy burden for the family (even with modern polyvinylchloride tubes) and psychologic and vital risks for the young patient.[18] Therefore, we chose 9 months as a delay prior to surgery. In cases of acquired LP, this delay can be reduced to 6 months if the origin of the trauma is known and seems irremediable (eg, inferior laryngeal nerve section). Our series of LP in children is reported briefly here, with details of our management of the surgical cases.

PATIENTS

Whole Group. From October 1974 to December 1985, 219 patients with LP have undergone examination and treatment in Bretonneau Pediatric Hospital in Paris. Of the 219 patients, 199 (91%) were neonatal, ie, diagnosed and initially treated during the neonatal period, as defined in France as the first 28 days after birth. Of this whole group, 88% of patients were dyspneic (29% in respiratory distress), 65% presented with stridor (noise), 39% with a weak or hoarse voice, and 29% with feeding difficulties. Direct laryngoscopy with use of telescopes and then a flexible fiberscope was always per-

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TABLE 1. CAUSES OF LARYNGEAL PARALYSIS IN 219 CASES

	Unilateral	*Bilateral*	*Total*
Idiopathic	44	53	97 (44%)
Neurologic	18	26	44 (20%)
Obstetric trauma	30	7	37 (17%)
Postoperative	31	4	35 (16%)
Vascular ring	4	0	4 (2%)
Unknown*	0	2	2 (1%)
Total	127	92	219

*Insufficient data available in charts.

formed (and sometimes repeated to verify the diagnosis) without general anesthesia. Ninety-two cases (42%) were bilateral abductor paralysis (Table 1). Of the 127 unilateral cases, 36 were right-sided and 91 were left-sided. The cause of such pediatric LP is sometimes difficult to discern. In cases of neurologic disorder, the cause of the LP is clear for encephalomeningocele and polyneuropathy, but less clear for corpus callosum agenesis or simple hypotonia, for example. Ninety-seven cases (44%) remain without any historical, clinical, or radiographic evidence suggesting an etiologic diagnosis and are denoted idiopathic. Concerning the follow-up, we have lost contact with 52 patients (23.7%). Of the remaining 167, 89 (53.3%) have had a spontaneous recovery, all within the first 3 months. Most of these were observed in the unilateral, idiopathic, and obstetric trauma cases. Forty-one patients tolerated their disease very well, with normal growth and activity, in spite of a persistent degree of poor mobility at laryngoscopy (vocal cords in paramedian position). Ten patients died, but none because of the laryngeal disease: nine died of their neurologic problems, and one of the consequences of the thoracic operation that led to the LP.

Finally, 27 patients did not tolerate their disease because of tremendous dyspnea and required repeated endotracheal intubation and/or tracheotomy. Of these cases, three patients remained with a tracheostomy tube alone because of severe neurologic disorders, and two patients later required a laryngotracheoplasty prior to decannulation because of associated postintubation subglottic stenosis. Thus, 22 patients underwent only vocal cord surgery and are reported below.

Surgical Cases. The preoperative features of the 22 cases are shown on the left side of Table 2. Most of the surgical cases were bilateral. Unilateral cases, all of them associated with neurologic problems, involved respiratory distress or repeated episodes of so-called croup and failure to thrive. No obstetric trauma or vascular ring compression case required surgical intervention. In two cases, LP appeared just after thoracic surgery (esophageal replacement for

TABLE 2. SURGICAL CASES

Case	*Age at Onset of Symptoms*	*Unilateral or Bilateral*	*Cause*	*Preop Trach*	*Age at Surgery*	*First Procedure*	*Initial Outcome*	*Second Procedure*	*Final Outcome*	*Postop Delay Until Decan/ Extub*
1	6 mo	B	I	–	2.5 yr	R Ectomy	Dyspnea	—	Stridor, dyspnea	8 d
2	1 d	B	I	–	6 mo	R Ectomy	Dyspnea	Cordopexy	Dysphonia	1 mo
3	3 yr	B	P	+	3.5 yr	R Pexy	Slight aspiration	—	Slight dysphonia	11 d
4	4 mo	B	I	+	3 yr	R Pexy	OK	—	OK	7 d
5	1 mo	B	I	–	14 yr	R Pexy	Dysphonia	—	OK	0 d
6	1 d	B	I	–	1 yr	R Pexy	OK	—	OK	0 d
7	1 d	B	I	+	10 mo	R Pexy	Aspiration	—	OK	27 d
8	2 d	B	I	–	3 yr	R Pexy	OK	—	OK	1 d
9	5 yr	B	N	–	7 yr	R Pexy	OK	—	OK	1 d
10	23 mo	B	P	+	2.5 yr	R Pexy	Dyspnea	Re-trach	Dysphonia	2 mo
11	2 d	B	I	–	3.5 yr	R Pexy	Dyspnea	Trach	Stridor	6 d
12	1 d	B	I	–	19 mo	R Pexy	OK	—	OK	1 d
13	1 d	B	I	–	3 yr	R Pexy + Trach	OK	—	OK	6 d
14	1 d	B	I	–	4 yr	R Pexy	OK	—	OK	0 d
15	1 d	B	N	+	1 yr	R Pexy + CP Myotomy	Aspiration	—	Aspiration	4 yr
16	1 d	B	I	+	3 yr	R Pexy	Dysphonia	—	OK	2 mo
17	14 yr	L	N	+	15 yr	L Ectomy	Slight dyspnea	—	OK	11 d
18	1 yr	L	N	–	4 yr	L Pexy	Dysphonia	—	OK	1 d
19	1 d	R	N	+	18 mo	R Pexy	Slight aspiration	—	OK	20 d
20	1 d	R	N	–	13 yr	R Pexy	OK	—	OK	0 d
21	8 d	L	N	–	2.5 yr	L Pexy	Slight dyspnea	—	OK	0 d
22	13 yr	L	N	+	14.5 yr	L Pexy	OK	—	OK	1 d

Decan — decannulation, Extub — extubation, B — bilateral, L — left, R — right, I — idiopathic, P — postsurgical, N — neurologic, Trach — tracheotomy, Ectomy — arytenoidectomy, Pexy — arytenoidopexy, CP — cricopharyngeal, Re-trach — tracheotomy again after first decannulation.

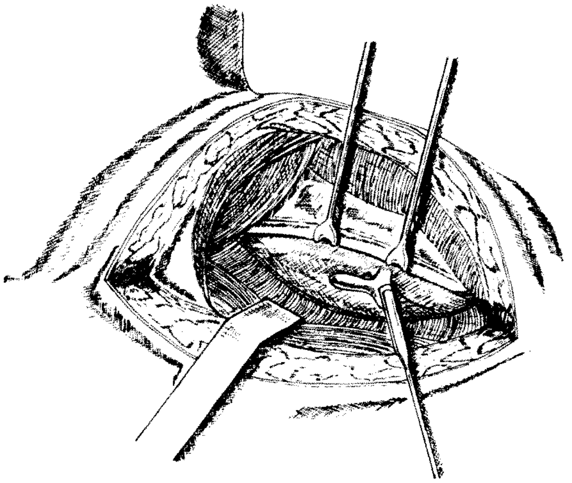

Fig 1. Muscle fibers are removed from posterior part of vocal process of arytenoid cartilage. Head of patient is on left.

caustic ingestion in one case, persistent ductus arteriosus plus coarctation of the aorta in the other). These are denoted postsurgical cases. The patients who did not undergo a tracheotomy had experienced severe and recurrent or progressive dyspnea — with permanent hypercapnia and hypoxia that led to multiple endotracheal intubations — before arriving at our institution.

One early case (case 2) was treated by surgery only 6 months after onset of the paralysis because of the lack of appropriate facilities at that time for a small tracheotomized child. Except for this patient and the two postsurgical cases (see Discussion), all the patients waited at least 10 months between onset and surgery.

TECHNIQUES

Two surgical techniques were used in these 22 patients. First, we performed the arytenoidectomy technique through a posterolateral external approach as described by Woodman.[12]

After a lateral cervical skin incision and posterior retraction of the sternomastoid muscle, the pharyngeal inferior constrictor muscle is divided vertically, parallel to the posterior border of the thyroid ala, which is left intact. The mucosa of the hypopharynx is separated from the inner side of the thyroid cartilage, and a part of the cricoid is discovered, close to the cricoarytenoid joint. In children, the thyroid cartilage is soft enough so that the ala can be pulled widely anteriorly without cutting the inferior cornu or dislocating the cricoarytenoid joint. The arytenoid cartilage is easy to discover and to remove if the patient's larynx is intubated. A cordopexy is associated with this technique; it involves passing a nonabsorbable suture through the submucosal layer of the posterior third of the vocal cord. This suture then is passed through the thyroid ala and knotted.

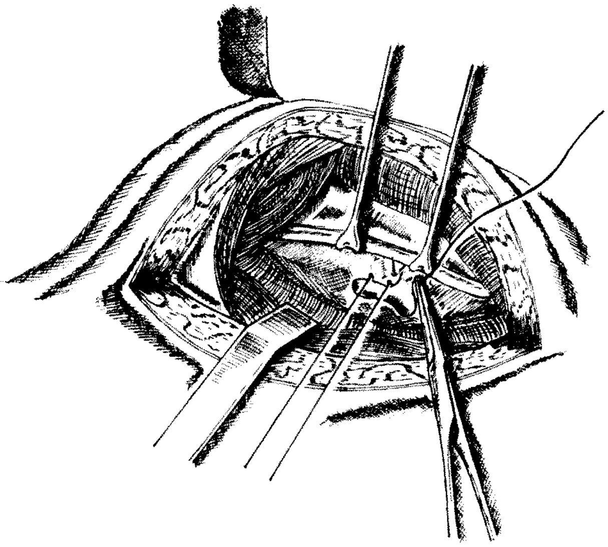

Fig 2. Two sutures pull body of arytenoid outward. Third suture is passed beyond vocal process.

Second, after two consecutive failures of the latter technique, we chose to perform arytenoidopexy. This is a variant of King's technique.[14] The approach is the same as in arytenoidectomy. In cases of bilateral paralysis, we chose the right side, which is easier for a right-handed operator.

Two main points are particular to children and must never be forgotten. One is that the cricoarytenoid joint must not be touched. This is the only solid point at which the thyroid ala is maintained. It prevents impaction of the thyroid cartilage while stabilizing the lateralized arytenoid. Second, the larynx should always be intubated before operation. This allows eversion of the vocal process, facilitating the placement of a suture at its level. Besides, it allows correct positioning of the arytenoid in the desired postoperative position.

The body, the upper part of the arytenoid, and the cricoarytenoid joint are visualized after removal of some fibers of the cricoarytenoid muscle (Fig 1). Two solid nonabsorbable sutures are passed around the body of the arytenoid, pulling it outward. Then, a third suture holds the vocal process as anterior as possible (Fig 2). The three sutures are passed through the thyroid cartilage with a figure eight crossing and knotted without placing any traction on the arytenoid, but merely holding it in position. Section of the interarytenoid muscle (in two cases) and the cricopharyngeal muscle (in one case) did not have any particular benefit.

The pharyngeal constrictor muscle then is repaired, and the wound closed on a suction drain. No damage has been done to the airway mucosa or the cartilaginous laryngeal skeleton. Postoperative extubation or decannulation usually can be expected immediately or within the first hours or days.

RESULTS

The type of surgery and results for each patient are described on the right side of Table 2. Arytenoidectomy was chosen initially for three patients of the series (cases 1, 2, and 17). One patient (case 17, 15 years old) had good results, but the two infants experienced postoperative stridor and dyspnea. One of them (case 1) required repeated steroid therapy. Improvement came progressively, probably with the larynx's growth. The other patient (case 2) required a second procedure (reinforced cordopexy) after 4 weeks. He then had good tolerance of extubation. At that time we probably underestimated the need for a strong associated cordopexy in this procedure in infants, and we decided to adopt the arytenoidopexy technique for the other cases.

Of the 22 cases, good results were achieved easily in 15 cases: immediate or rapid extubation (first hours or days) or decannulation (first week). In two cases, a temporary postoperative edema led to a tracheotomy for a couple of days. Two patients experienced feeding difficulties with aspiration pneumonia. This delayed the decannulation for 1 month in the first patient, and for 4 years in the other, who presented with cricopharyngeal achalasia. As sequelae, we noted one case of minimal liquid-feeding difficulties and four cases of slight dysphonia.

DISCUSSION

The clinical and endoscopic data of our series of LP in infants and children are comparable to those of the other series previously reported.[3,4,6,15] The details of our 219 patients can be found in another report.[19]

Concerning the management of persistent cases of dyspnea, we adopted a resolute surgical attitude. Most neonatal cases resolve spontaneously in the first months, as we saw. But in case of no spontaneous recovery or improvement after 6 to 9 months of follow-up, we believe that a tracheotomy tube should not remain longer. Considering the vital risk and the psychologic and socioeconomic burden of long-term tracheotomy in infants,[18] we have been convinced that this problem has a surgical solution.

Of the techniques proposed, the reinnervation of the posterior cricoarytenoid muscle[9] has not proven its efficacy in all hands.[3,10] The endoscopic techniques[15] have seldom been used in young infants and seem much more difficult to apply here than in adults. Arytenoidectomy[2,12,13] is an excellent procedure, but it tends to leave an empty posterior hemilarynx with a flaccid aryepiglottic fold that may become obstructive. We had failures in two infants with this procedure, probably because of an insufficient cordopexy. However, this led us to adopt the arytenoidopexy procedure for children. The results of our series demonstrate this is quite suitable in these patients.

The "pexy" techniques, which lateralize the laryngeal structures, seem at least as efficient in widely and surely opening the narrow infant glottis[8,14] as arytenoidectomy. Since they are perfectly feasible through an external approach, we do not advocate using the endoscopic technique.

We slightly modified the King[14] technique and adapted it to the softness of the infant's laryngeal cartilages. If the thyroid ala is just pulled outward and forward but left intact — without any section or disjunction — a solid point exists for securing the lateralized arytenoid. The pitfall of this method seems to be an excessive opening of the glottis with possible feeding difficulties and weak voice. These temporary troubles may be avoided by the preoperative use of a small endotracheal tube. Finally, we think that every infant or child with LP and persistent major dyspnea has to be decannulated. In addition to arytenoidectomy, arytenoidopexy seems well adapted to this purpose.

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MICROVASCULAR DECOMPRESSION BY RETROSIGMOID APPROACH FOR TRIGEMINAL NEURALGIA: EXPERIENCE IN 200 PATIENTS

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Trigeminal neuralgia is often seen in elderly persons. Two hundred patients with trigeminal neuralgia were submitted to microvascular decompression by a retrosigmoid approach. The surgical procedure is described. Vascular compression of the nerves was noticed in all these patients at operation. One hundred ninety-seven had relief of symptoms postoperatively, for a 98.5% cure rate. In addition, we suggest that another important cause is arteriosclerosis.

KEY WORDS — microvascular decompression, retrosigmoid approach, trigeminal neuralgia.

Primary trigeminal neuralgia is commonly seen in elderly persons. In 1962, Gardner[1] first described neurovascular decompression for treating hemifacial spasm, and others have reported a similar surgical procedure with some modifications for treatment of trigeminal neuralgia.[2-5] Otoneurosurgeons usually prefer the posterior labyrinthine approach for decompression. We have treated 204 cases of primary trigeminal neuralgia, four of which were found intraoperatively not to be caused by vascular compression. We report 200 cases of primary trigeminal neuralgia in which microvascular decompression was accomplished by a retrosigmoid approach between April 1985 and January 1988.

PATIENTS AND METHODS

Of the 200 patients with primary trigeminal neuralgia, 109 were men and 91 were women. Ages ranged from 38 to 80 years, with an average of 57 years. One hundred sixty patients were between 51 and 80 years old (80%). The course of disease was from 1.5 to 15 years, with an average of 9.5 years. One hundred three cases were right-sided and 97 were left-sided. The branches involved were maxillary alone in 40 cases, frontal and maxillary in 26 cases, mandibular in 30 cases, maxillary and mandibular in 84 cases, and all three in 20 cases.

There were 91 cases of mild hypertension (45.5%; diastolic blood pressure, 90 to 100 mm Hg). Blood cholesterol was at or over 240 mg% in 75 cases (37.5%). Blood-lipid glycerides were at or over 90 mg% in 94 cases (47%). Funduscopy showed arteriosclerosis in 165 cases (82.5%).

The symptoms varied among sufferers, from a few to many seizures daily. No patient was relieved by any medical regimen attempted.

The patient's head was positioned for a routine mastoid operation, and local anesthetic was given. A C-shaped incision on the right (and reverse C on the left) was made behind the hairline slightly above the mastoid border; a 3-cm square skin pedicle flap, including subcutaneous and muscular tissue, thus was elevated and sutured anteriorly. Two hundred fifty milliliters of intravenous mannitol 20% was given rapidly at this stage. By bone drilling, craniotomy then was performed, and the bone chips were preserved for future use. A bony window 1.5 to 2 cm was made anteriorly to expose the posterior margin of the sigmoid sinus, and superiorly to expose the inferior margin of the transverse sinus. As the intracranial pressure had dropped by this time, the patient's head was elevated about 30°, and a U-shaped piece of dura, similar to the bone window, was cut and turned in the direction of the sigmoid sinus. The circumference of cerebellum exposed was about 1 to 1.5 cm in diameter. Under an operating microscope, the cerebellum was pressed lightly downward along the tentorium so that the petrosal vein was visible. The pontine-cisternal arachnoid was cut between the eighth cranial nerve and the petrosal vein, and CSF was sucked out as far as possible. The fifth cranial nerve with its anatomic relationships was then clearly visible. The nerve was examined carefully, from the periphery up to the root, with particular attention paid to the pontine root entry zone. The blood vessel pressing upon the nerve root was well defined and gently dissected from the nerve root, and a small piece of muscle then was inserted between the two. The surgical field then was washed with warm normal saline. Bleeding was controlled, and the dura sutured with a Gelfoam covering. The bony window and posterior perisinus mastoid air cells were filled with bone chips. The wound was sutured layer by layer, and a pressure dressing applied.

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RESULTS

The trigeminal nerve was compressed by superior cerebellar arteries in 117 cases, by a vascular loop in 69 cases (among which in 19 cases it was compressed by two to three collateral branches), and by an aneurysm in two cases; and in 12 cases the nerve was entangled with veins.

Twenty-four cases were followed for 3 to 6 months, 27 cases for 7 to 12 months, and 149 cases for 13 to 34 months. Except for three cases of symptom recurrence within 6 months, all patients are free of symptoms, for a 98.5% success rate. The neurologic symptoms disappeared in all patients immediately following operation.

Following surgery no patients had meningitis or CSF leaks. In 27 cases herpes of the lip occurred but disappeared rapidly. There was no mortality or major morbidity in this series.

DISCUSSION

Dandy[6] was the first to suggest that arterial compression might be one of the causes of trigeminal neuralgia. Gardner[1] advocated this idea as well in 1962. In 1977, Jannetta et al[2] reported on neurovascular decompression. Arterial compression as a cause gradually became better recognized.[4,5,7,8]

Most of the primary trigeminal neuralgia cases are due to compression of the nerve roots by blood vessels, as confirmed by abundant clinical reports. Blessing[7] reported that 86% of 390 cases of trigeminal neuralgia were due to vascular compression, and that the remaining 14% were due to tumor growth. Most of the vascular compressions were located at the root entry zone of the pons, and therefore Blessing insisted on the exploration of that particular portion of the nerve during the operation.[7] Among the 200 primary trigeminal neuralgia patients reported here, we noticed all had evident vascular compression of the nerves. Therefore, vascular compression seems to be the main cause of trigeminal neuralgia. In addition, we found clinical evidence of arteriosclerosis in 82.5% of the patients, the damage to the nerve caused by arteriosclerosis being more severe. This suggests a second important cause of primary trigeminal neuralgia.

The retrosigmoid approach has several advantages. First of all, it is suitable for various other kinds of operations around the cerebellopontine angle, such as those for excision of tumors, tinnitus, positional vertigo[9,10] originating from the vascular loop syndrome, and idiopathic glossopharyngeal neuralgia. The approach is particularly suitable when a labyrinthine approach is contraindicated in a sclerotic mastoid bone, in the presence of an anteriorly positioned sigmoid sinus, and in cases complicated by chronic otitis media with a danger of direct communication between the middle ear and the subarachnoid space. Second, the operating field is large enough, and if necessary, the bony window may be enlarged further upward, downward, or posteriorly. Bleeding can be controlled easily under direct vision. Third, as the operating field is not transmastoid and the bony window and perisinus air cells of the lateral sinus posterior can be filled with bone chips, CSF otorrhea should not occur. Fourth, there will be no interference with the endolymphatic sac, the posterior semicircular canal, or the vestibular aqueduct.

Since microvascular decompression removes the cause, the cure rate may be as high as 98%, and the recurrence rate is low. Dissection of blood vessels from the underlying nerve is not difficult. We use a piece of muscle of the patient as an insert between nerve and vessel for long-lasting effect.

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VESTIBULO-OCULAR REFLEX AS A PARAMETER OF SEASICKNESS SUSCEPTIBILITY

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The vestibulo-ocular reflex (VOR) is known to be modulated in response to changing vestibular and optokinetic stimuli. The purpose of this study was to investigate possible relationships between VOR and future susceptibility and habituation to seasickness. Thirty candidates for future maritime service were exposed to a series of yaw axis smooth harmonic accelerations before and after 6 months of regular sailing, and their VOR gain and phase responses were recorded. Seasickness severity was estimated after 1 and 6 months of service by a questionnaire. We conclude that VOR gain at 0.01 Hz may serve as a physiologic correlate helping to predict seasickness susceptibility, and that the increase in phase lead at 0.02 Hz may mark the habituation process to sea conditions.

KEY WORDS — seasickness, vestibular habituation, vestibulo-ocular reflex.

INTRODUCTION

Seasickness is very common among naval personnel. Sixty percent to 90% of inexperienced sailors suffer from seasickness, while 15% to 60% of experienced crew members are affected.[1] Seasickness becomes a major problem in modern seamanship, in which small crews are responsible for the operation of sensitive and sophisticated equipment.

Objective physiologic criteria for the prediction of future susceptibility to seasickness and the estimation of habituation to sea conditions would be of the utmost importance in the selection of naval personnel.

The neural mismatch and sensory rearrangement theory is accepted currently as an explanation of motion sickness causation and pathogenesis.[1,2] According to this theory, motion sickness symptoms will emerge when vestibular, ocular, and proprioceptive receptors stimulated by motion produce associated signals that are at variance with the associated inputs expected on the basis of past experience. The same mismatch signal brings about updating of the previously stored motion association cues. Thus, repetitive neural mismatch signals will ameliorate motion sickness symptoms caused by the specific motion stimulus.

Two main types of motion cue mismatch can be identified according to the sensory systems involved: one is a visual-vestibular mismatch, and the other a canal-otolith mismatch.[3]

TABLE 1. SEASICKNESS SEVERITY SUBGROUPS AFTER 1 MONTH OF SAILING

	Scale of Wiker et al[12,13]								
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*Total*
No. of subjects	1	6	1	2	3	0	1	16	30

The vestibulo-ocular reflex (VOR) is the main physiologic mechanism responsible for stability of the visual field on the retina. Head acceleration transduced by the vestibular apparatus of the inner ear produces compensatory conjugated eye movements, which move at the same speed as the head but in the opposite direction. This normally keeps images from moving on the retina during head movements, and allows us to move and see at the same time.[4] The VOR parameters are compatible with natural motion patterns.

Altered relationships between vestibular and visual sensations, as caused by wearing reversing prisms, soon result in visual-vestibular conflict. The VOR, being inappropriate to the new conditions, leads to image slip on the retina and the development of motion sickness symptoms.[5] The VOR finally becomes adapted to the unnatural optokinetic or vestibular stimuli, as has been demonstrated in several mammalian species as well as in humans.[5-9] Reorganization of the eye movements, in order to reduce or abolish image motion on the retina during head turning, is followed by the disappearance of motion sickness symptoms.[6,9]

TABLE 2. MODIFIED SEASICKNESS SEVERITY CLASSIFICATION

	Modified Scale			
	A	*B*	*C*	*Total*
Scale of Wiker et al[12,13]	0, 1, 2	3, 4, 5, 6	7	
No. of subjects	8	6	16	30

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TABLE 3. GAIN AND PHASE VALUES (MEAN ± SD) AT SHA 1

Frequency (Hz)	*Gain*	*Phase (°)*
0.01	0.316±0.12	47.74±9.43
0.02	0.531±0.22	29.90±7.73
0.04	0.554±0.21	17.25±8.80
0.08	0.563±0.23	5.83±8.89
0.16	0.630±0.20	0.69±6.66

SHA 1 — first smooth harmonic acceleration test, conducted before subjects' exposure to sea.

TABLE 4. ANOVA OF VOR PARAMETERS AT SHA 1 AMONG SEASICKNESS SEVERITY CATEGORIES AFTER 1 MONTH OF SAILING

VOR Parameter	*Frequency (Hz)*	*F (27, 2)*	*Significance*
Gain	0.01	16.322	0.000 (S)
	0.02	5.006	0.014 (S)
	0.04	4.033	0.029 (S)
	0.08	4.017	0.015 (S)
	0.16	1.608	0.218 (NS)
Phase (°)	0.01	1.948	0.160 (NS)
	0.02	1.855	0.174 (NS)
	0.04	0.114	0.877 (NS)
	0.08	1.047	0.366 (NS)
	0.16	0.488	0.624 (NS)

ANOVA — analysis of variance, VOR — vestibulo-ocular reflex, SHA 1 — first smooth harmonic acceleration test, conducted before subjects' exposure to sea, 27 — residual degrees of freedom, 2 — explained degrees of freedom, S — significant, NS — not significant.

The purpose of this study was to examine possible relationships between basic VOR parameters and future susceptibility to seasickness, and to learn whether VOR changes take place in accordance with habituation to the sea.

MATERIALS AND METHODS

Thirty-nine male candidates for future maritime service, ranging in age from 18 to 20 years, gave written informed consent and participated in the study. It was established by history, physical examination, and audiogram that all subjects had normal visual, audiovestibular, and neurologic function. None had ever sailed previously.

The VOR was evaluated by the smooth harmonic acceleration (SHA) test as described by Wolfe et al.[10,11] Medications and alcohol were restricted 48 hours prior to the test date. The SHA tests were carried out with the Contraves-Goerz DP-300 computerized rotatory chair system (Neurokinetics, Inc, Pittsburgh). Each subject was seated in a chair mounted on the shaft of a computer-controlled torque motor, and rotated about the yaw axis at five frequencies at octave intervals from 0.01 to 0.16 Hz. The stimulus paradigm consisted of four complete cycles at 0.01 Hz and eight complete cycles at the other frequencies. The rotational velocity varied sinusoidally, with a peak velocity of 50°/s, where the angular acceleration ranged from 3.8°/s/s to 60°/s/s. A headrest was provided that held the head tilted 30° forward, thus bringing the horizontal semicircular canal plane perpendicular to the axis of rotation. All tests were conducted in complete darkness, with the subjects wearing black-painted goggles to eliminate any visual cues. Alertness was assured by continuous conversation and questions. The subjects were instructed to avoid gaze fixation during rotation. Standard electronystagmographic techniques were employed to record the resulting summated horizontal nystagmus, and the responses were stored in the system's computer. The slow phase velocity of the nystagmus was extracted and compared with the chair's motion data to obtain the gain, phase, and spectral purity parameters of the subject's VOR for each of the frequencies tested.

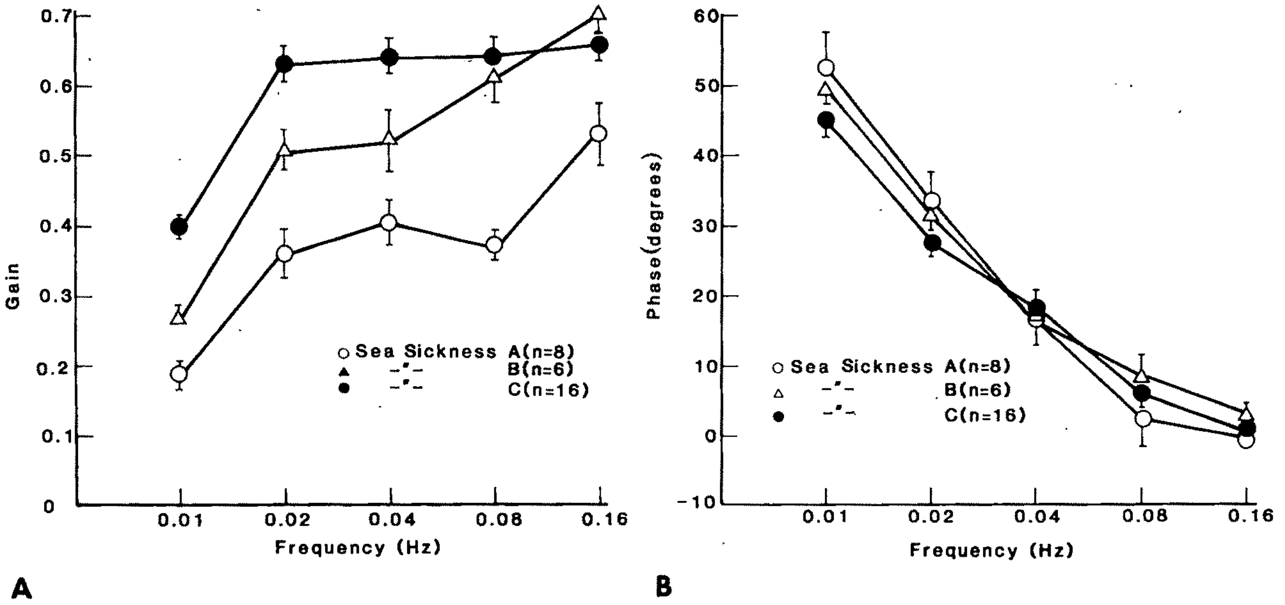

Fig 1. Vestibulo-ocular reflex values (mean ± SEM) for three seasickness severity categories (see Tables 1 and 2). A) Gain. B) Phase.

TABLE 5. SUMMARY OF MULTIPLE REGRESSION STEPS FOR SEASICKNESS SEVERITY WITH VOR PARAMETERS AT SHA 1

Variable	*Multiple* *r*	r^2	r^2 *Change*	*Simple* *r*
Gain 0.01 Hz	0.701	0.492	0.492	0.701
Gain 0.04 Hz	0.712	0.507	0.015	0.090
Phase 0.02 Hz	0.735	0.540	0.033	−0.338
Gain 0.16 Hz	0.737	0.544	0.004	0.168
Gain 0.04 Hz	0.740	0.548	0.004	0.440
Phase 0.01 Hz	0.742	0.551	0.003	−0.331
Phase 0.08 Hz	0.743	0.553	0.002	0.092
Gain 0.08 Hz	0.744	0.554	0.001	0.370
Phase 0.16 Hz	0.747	0.558	0.004	−0.014

Variable gain 0.02 Hz was excluded by SPSS-11 software, as it did not meet default criteria for inclusion in regression equation (F = 0.01, minimum tolerance = 0.001).

VOR — vestibulo-ocular reflex, SHA 1 — first smooth harmonic acceleration test.

The VOR gain is the ratio of the eye's maximal slow phase velocity to the maximal head rotation velocity. As the subject's head was leaning against the chair, the head and chair motion parameters were identical.

The phase is a measurement of the eye's movement timing relative to the head velocity input. It is expressed in the number of degrees by which eye motion lags behind head motion.

Spectral purity is the percentage of the slow phase output power that is at the stimulus frequency. The remainder of the response is harmonic distortion or noise. Only if the spectral purity is greater than 75% can the gain and phase be considered accurate descriptors of the VOR.

All 39 subjects underwent a first SHA test before their actual exposure to the sea (SHA 1). At this stage, nine of the participants were excluded from the study because of spectral purity values lower than 75%. Seasickness severity in the remaining 30 subjects was estimated after 1 month of regular service at sea by use of a questionnaire adopted from Wiker et al.[12,13] The validity and reliability of this questionnaire were proved to be high in a seasickness survey conducted by the US Coast Guard.[12,13]

We checked whether individuals with different levels of seasickness severity differ as to their VOR gain and phase characteristics. Correlations between the basic VOR parameters and future susceptibility to seasickness were examined.

Twenty-nine subjects did a second SHA test (SHA 2) and completed a questionnaire after 6 months of regular sailing. One subject was lost to follow-up for administrative reasons. Gain and phase values before and after exposure to sailing were compared. Possible correlations between habituation to the sea and variation in VOR parameters were looked for. The statistical analysis was carried out with SPSS-11 software and a PDP 11/23 computer.

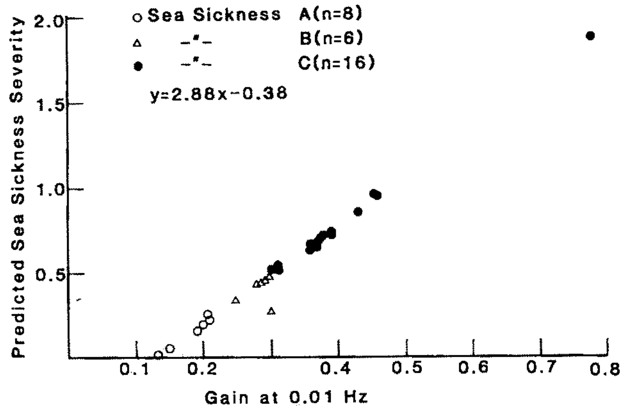

Fig 2. Predicted seasickness severity versus vestibulo-ocular reflex gain at 0.01 Hz for three seasickness severity categories (see Tables 1 and 2).

RESULTS

Table 1[12,13] summarizes the number of subjects included in each of the seven categories of seasickness as described by Wiker et al.[12,13] As some of the seasickness severity categories contained few subjects, a division into three modified categories was made. The modified classification appears in Table 2.[12,13]

The average values of gain and phase responses to the different frequencies tested in SHA 1 are presented in Table 3. Figure 1 illustrates these values for the three seasickness severity subgroups.

One-way analysis of variance (ANOVA) was applied in order to identify VOR parameters that might differ among the three subgroups (Table 4). The variance of VOR gain values at 0.01 to 0.08 Hz was found to be significantly different. Lower VOR gain values at these frequencies were associated with less susceptibility to seasickness as reported after 1 month of sailing. However, VOR gain at 0.16 Hz and phase lags at all frequencies examined did not differ among seasickness severity categories.

Stepwise inclusion multiple regression of seasickness severity with gain and phase values at SHA 1 was carried out in order to examine the amount of variance in seasickness severity explained by each of the VOR parameters, and to find out which of these

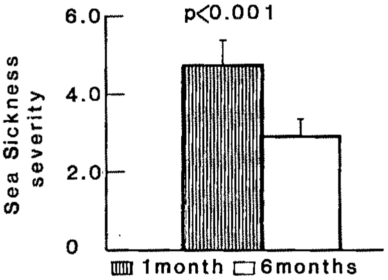

Fig 3. Seasickness severity (Wiker[12,13] scale; mean ± SEM) after 1 and 6 months of sailing.

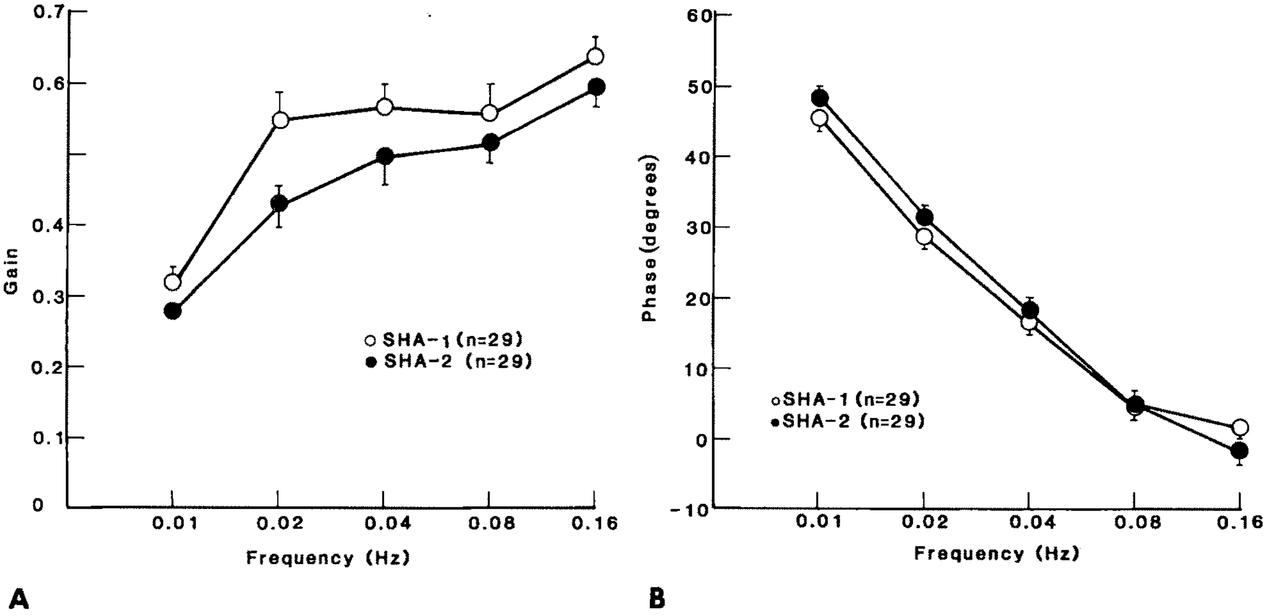

Fig 4. Vestibulo-ocular reflex values (mean ± SEM) before (SHA 1) and after (SHA 2) 6 months of sailing. A) Gain. B) Phase. SHA — smooth harmonic acceleration.

parameters may predict future seasickness susceptibility.

The independent variables, VOR gain and phase at the different frequencies tested, were included in the regression equation in descending order according to their relative contribution to the explanation of the variance in seasickness severity. A dichotomous criterion of Wiker grade 7/Wiker grades 0 to 6 was employed for the dependent variable (seasickness severity). Table 5 summarizes the regression steps.

It appears that most of the variance in seasickness severity is explained by the VOR gain response to the 0.01-Hz oscillation. The contribution of the remaining parameters to the explanation of the variance is minor. The distribution of VOR gain values at 0.01 Hz for the three categories of seasickness severity on the regression line is illustrated by Fig 2.

The mean seasickness severity after 1 month of sailing, which was 4.75 according to the Wiker scale, decreased to 2.89 after 6 months of exposure to open sea conditions. This difference between the means was statistically significant ($p<.001$; $t = 4.78$, paired t test) (Fig 3[12,13]).

Figure 4A illustrates the mean gain values for the study population as measured in SHA 1 and SHA 2, and Fig 4B illustrates the parallel phase values.

Paired t tests were used to examine whether significant modulations of VOR parameters took place after 6 months of sailing. A significant reduction of VOR gain at 0.01 ($p<.05$) and 0.02 Hz ($p<.005$), as well as a significant increase in phase leads at 0.01 ($p<.05$), 0.02 ($p<.001$), and 0.04 Hz ($p<.05$), was found (Table 6 and Fig 5).

The change (Δ) in the mean values of gain and phase between SHA 1 and SHA 2 was calculated for all the frequencies tested. Possible correlations between these measurements and the differences in seasickness severity after 6 months and 1 month of sailing were examined. Table 7[12,13] summarizes the

TABLE 6. COMPARISON OF VOR PARAMETER VALUES (MEAN ±SD) AT SHA 1 AND SHA 2 (PAIRED *T* TEST)

VOR Parameter	*Frequency (Hz)*	*SHA 1*	*SHA 2*	*Significance*
Gain	0.01	0.32±0.13	0.28± 0.09	p<.05
	0.02	0.54±0.20	0.43± 0.19	p<.005
	0.04	0.56±0.17	0.50± 0.22	NS
	0.08	0.56±0.22	0.51± 0.19	NS
	0.16	0.63±0.20	0.59± 0.19	NS
Phase	0.01	46.58±9.39	48.67± 8.40	p<.05
	0.02	28.70±7.24	32.01± 6.59	p<.001
	0.04	16.68±9.30	18.46± 8.55	p<.05
	0.08	5.19±9.80	5.16± 8.42	NS
	0.16	1.83±5.97	− 1.24±10.43	NS

VOR — vestibulo-ocular reflex, SHA 1 — first smooth harmonic acceleration test, SHA 2 — second smooth harmonic acceleration test, NS — not significant.

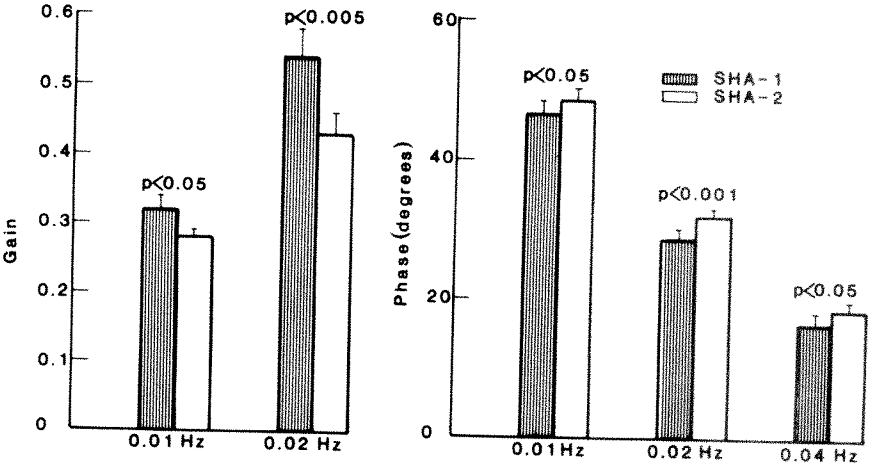

Fig 5. Significant differences in vestibulo-ocular reflex parameters before (SHA 1) and after (SHA 2) 6 months of sailing (mean±SEM). SHA — smooth harmonic acceleration.

calculated Pearson product-moment correlation coefficients and their statistical significance. The only significant correlation found was between decreased seasickness severity and increased phase lead at 0.02 Hz (r = −0.396; p = .02).

DISCUSSION

The VOR gain values at 0.01-, 0.02-, 0.04-, and 0.08-Hz sinusoidal oscillations, measured before exposure to sea conditions, were significantly different for the three levels of seasickness severity as reported after 1 month of sailing. Most of the variance in seasickness severity after 1 month of sailing was explained by the VOR gain response to the 0.01-Hz oscillation at SHA 1.

A significant mean reduction of seasickness severity took place after 6 months of sailing. In parallel with this habituation to sea conditions, a significant diminution of VOR gain responses was found for 0.01 and 0.02 Hz, as well as increased phase leads at 0.01, 0.02, and 0.04 Hz. The decrease in seasickness symptoms was significantly correlated with the increased phase lead at 0.02 Hz.

It has been well established that the VOR plays a major role in stabilizing the eyes in inertial space during both internally and externally generated head movements.[4,14] Altered relationships between vestibular and visual sensations caused by unnatural motion patterns are a major precipitating factor for the symptoms of motion sickness.[3]

It has been suggested that under such conditions the existing VOR is no longer appropriate and must be modified or suppressed in order to abolish vestibulo-ocular mismatch and the consequent development of motion sickness. Various reports document VOR gain and phase modifications in response to induced vestibulo-ocular conflict, but none deals with the specific topic of seasickness. Plastic adaptation of VOR gain to magnifying or reversing spectacles, sufficient to abolish the vestibulo-ocular conflict that induces ataxia, nausea, vomiting, and oscillopsia, has been demonstrated in several vertebrate species,[6-8,15,16] as well as in humans.[5,17-19] Monkeys repeatedly rotated with different sinusoidal frequencies, and humans rotated at 0.01 Hz, showed an increase in phase angle between stimulus and nystagmus slow phase velocity, and a concomitant decrease in gain.[9] After this modification process, all human subjects had a clearly raised threshold to motion sickness. Decreased VOR gain was demonstrated in weightlessness during voluntary and passive horizontal head rotations.[20,21] However, an apparently increasing phase lead with increasing gravity load could not be confirmed by statistical analysis.[21]

An interesting perspective is provided by the examination of the influence on the VOR of transdermally administered scopolamine and dimenhydrinate. These anti-motion sickness drugs were found to act at least partly by reducing the gain of the vestibular and optokinetic responses. This effect was of a magnitude similar to that of the diminution in experimental nausea and vertigo.[22,23]

Our observations that VOR gain decreases and phase lead increases at specific sinusoidal frequencies, in parallel with habituation to sea conditions, imply a vestibular habituation process. The finding that modulation of VOR parameters occurred only for oscillation frequencies of 0.04 Hz and less is confirmed by several studies on humans and other ani-

TABLE 7. CORRELATIONS BETWEEN DIFFERENCE IN MEAN VOR PARAMETERS AT 1 AND 6 MONTHS OF SAILING AND DECREASE IN SEASICKNESS SEVERITY

VOR Parameter	*Frequency (Hz)*	*Correlation Coefficient*	
Δ Gain	0.01	r = 0.201	(p = .14)
	0.02	r = 0.304	(p = .06)
	0.04	r = 0.153	(p = .22)
	0.08	r = −0.085	(p = .33)
	0.16	r = −0.031	(p = .43)
Δ Phase	0.01	r = −0.092	(p = .32)
	0.02	r = −0.396	(p = .02)
	0.04	r = −0.243	(p = .11)
	0.08	r = −0.276	(p = .08)
	0.16	r = 0.070	(p = .36)

Severity measured on Wiker[12,13] scale.

VOR — vestibulo-ocular reflex, Δ Gain — difference in mean gain values, Δ Phase — difference in mean phase values.

mal species. Habituation occurred only with a stimulus frequency below 0.05 to 0.1 Hz, at which some phase lead of the VOR already exists.[6,9,13]

The finding that some subjects not yet exposed to sea conditions had lower VOR gain values at 0.01 Hz, and were also less susceptible to seasickness, can be explained by the variability of the VOR characteristics in the normal population, and the modulations of the latter as a consequence of past motion experience. Such modulations were proved to be regulated by the cerebellar flocculus.[24]

In conclusion, the basic VOR gain in response to yaw sinusoidal oscillation at 0.01 Hz may assist in the selection of naval crew members. Modulations of VOR gain at 0.01 and 0.02 Hz and phase response to 0.01- to 0.04-Hz oscillations occur after 6 months at sea. The increase in phase lead at 0.02 Hz may be used to monitor the habituation process to sea conditions.

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CORRELATIVE IMAGING OF SPHENOID DYSPLASIA ACCOMPANYING NEUROFIBROMATOSIS

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Experience with five cases of sphenoid dysplasia is collected and illustrated by plain film, computed tomography, and magnetic resonance imaging. Ancillary changes in the maxilla and mandible are shown. Paramount to the presentation are changes induced in the orbit resulting in a large superior orbital fissure with or without a meningeal cyst projecting through the fissure. Serial studies of one patient from birth through 5 years of age present the progressive nature of this abnormality.

KEY WORDS — neurofibromatosis, sphenoid wing dysplasia, superior orbital fissure enlargement, temporal lobe enlargement.

INTRODUCTION

Sphenoid dysplasia is a rare but classic finding in neurofibromatosis, a clinically diverse syndrome affecting both neuroectodermal and mesenchymal tissues. The cause of neurofibromatosis remains unclear. Proposals of a multiple cell origin[1] and elevation of nerve growth stimulating activity[2] point to a fundamental pathophysiologic defect. Although an autosomal dominant pattern of transmission has been demonstrated, this occurs in only 50% of cases. The remainder are attributed to spontaneous occurrence.[3] The diagnosis therefore is based on finding the spectrum of clinical features. Typical changes include multiple patches of cutaneous pigmentation (café au lait spots), pedunculated subcutaneous nodules, and tumors arising from the neurilemmal sheath and neuroblasts of peripheral nerves.

Skeletal lesions are present in 30% to 50% of cases.[4,5] Some of these skeletal deformities are clearly associated with soft tissue tumors, while others occur independently. Underdevelopment of bone independent of pressure from an adjacent tumor may be a trophic change representing disturbances in nutrition, incident to faulty innervation, inadequate blood supply, or absence of work-producing stimuli.[4] Whether or not there is an associated tumor is not simply of academic interest. In the case of dysplasia of the sphenoid bone unnecessary operations, some with fatal outcome, have been performed.

The first radiographic description of sphenoid dysplasia in neurofibromatosis was by LeWald in 1933.[6] The importance of recognizing the defect of the orbit radiographically to avoid enucleation in search of tumor was presented clearly. A schematic drawing showing the defect of the superior orbital wall and replacement with a meningocele was provided.

Each of the patients discussed in this article presented with pulsatile exophthalmos. Failure of vision that is not correctable is also a classic feature of sphenoid dysplasia.[7] The exophthalmos of sphenoid dysplasia has been attributed to encroachment on the orbit by intracranial contents, and the pulsations to transmitted pulsations of the cerebrum.[8] Cases have been presented that involve direct contact of the temporal lobe with the orbital soft tissue

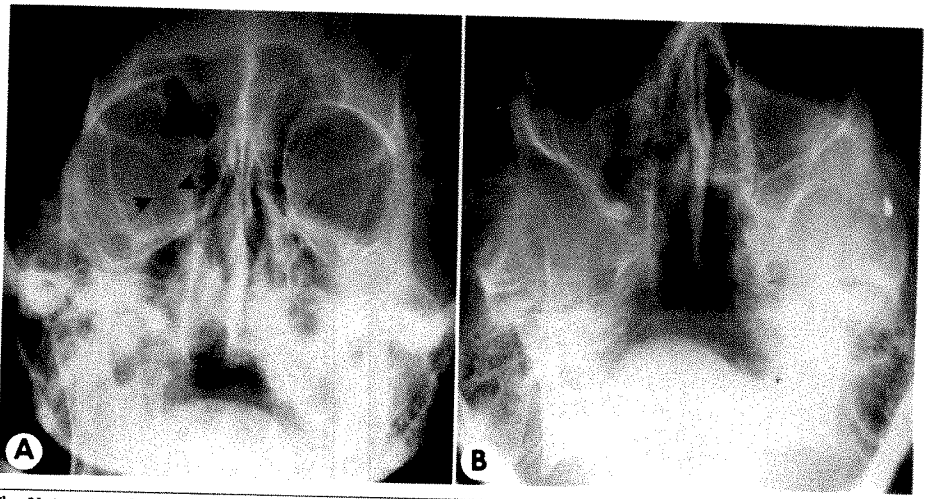

Fig 1. (Case 1) Right-sided sphenoid dysplasia. A) Caldwell view with right orbit enlargement. Symmetric increase in size of orbit rim and downward displacement of orbit floor are present. Superior orbital fissure is enlarged (arrowheads). B) Waters view shows accompanying hypoplasia of right maxilla, zygoma, glenoid fossa, and mandible.

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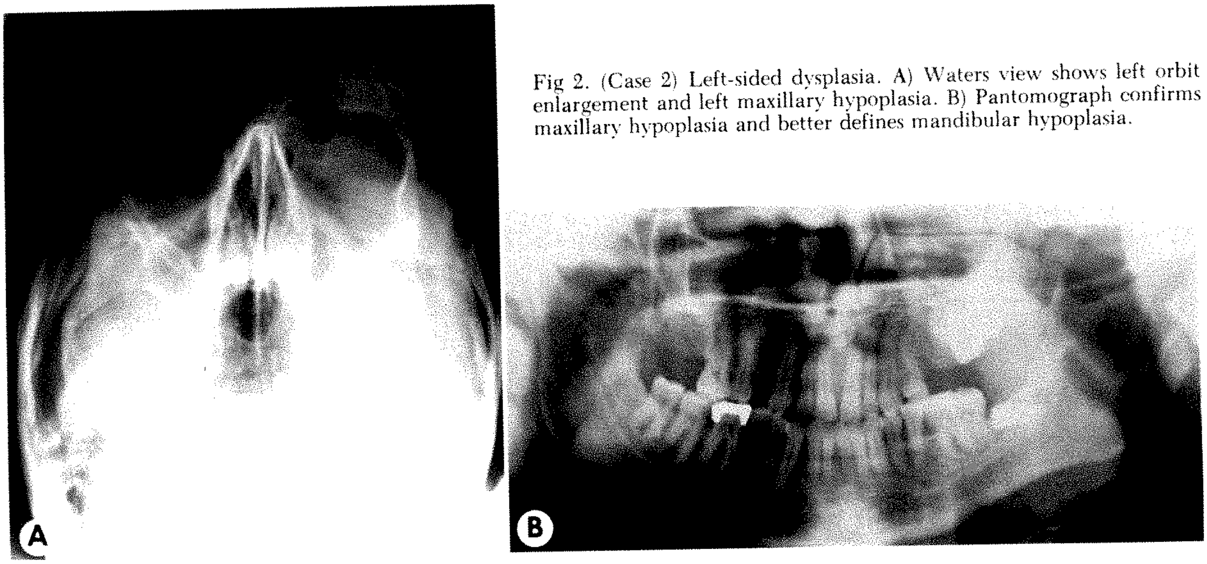

Fig 2. (Case 2) Left-sided dysplasia. A) Waters view shows left orbit enlargement and left maxillary hypoplasia. B) Pantomograph confirms maxillary hypoplasia and better defines mandibular hypoplasia.

by herniation through the defect.[5,9] Other authors describe filling of the orbital defect with a meningocele.[6] Confirmation of cases prior to computed tomography (CT) could only be obtained surgically and was not obtained once it became clear that surgery was necessary only for cosmetic repair. Exophthalmos also may indicate increased intracranial pressure in these patients, who are prone to a variety of intracranial tumors.

The incidence of sphenoid dysplasia has been reported at approximately 13.5% of neurofibromatosis patients.[7]

We present the x-ray, CT, and magnetic resonance imaging (MRI) findings in a group of our patients with sphenoid dysplasia. No previous report of the MRI findings in this disease has been found in the English literature.

CASE REPORTS

Case 1. A 54-year-old woman presented with right-sided pulsatile exophthalmos and facial and mandibular asymmetry. Figure 1 shows marked right orbital enlargement with downward displacement of the orbital floor. Hypoplasia of the right maxillary sinus and zygomatic arch, glenoid fossa, mandibular condyle, and coronoid process is present. Thinning of the vertical mandible ramus is also present. The horizontal ramus is normal in size.

Case 2. A 34-year-old woman had pulsatile exophthalmos on the left accompanied by facial and dental asymmetry. Figure 2 shows the left orbital enlargement. The left zygoma and maxilla are hypoplastic, as are the left mandibular condyle neck and coronoid process.

Case 3. An 18-year-old woman presented with pulsatile exophthalmus and periorbital plexiform neuromas. Figure 3 shows enlargement of the left orbit. The globe is low-lying, and the right maxillary sinus is small in comparison to the left. Nodular masses fill the retrobulbar portions of the orbit and

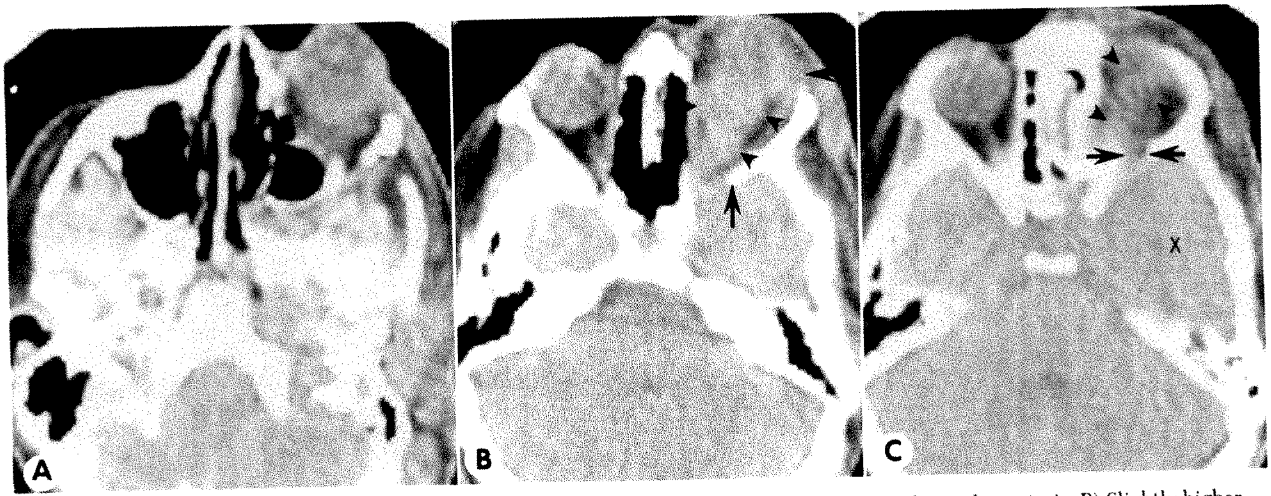

Fig 3. (Case 3) Left-sided dysplasia. A) Axial computed tomogram shows low position of left orbit and proptosis. B) Slightly higher axial CT reveals enhancing nodules throughout muscle cone (arrowheads) and periorbital soft tissue thickening due to plexiform neuromas (horizontal arrow). Left superior fissure is enlarged (vertical arrow). C) Higher view just under orbit roof shows more subcutaneous neuromas (arrowheads), widening of fissure (arrows), and enlargement of left temporal fossa (X).

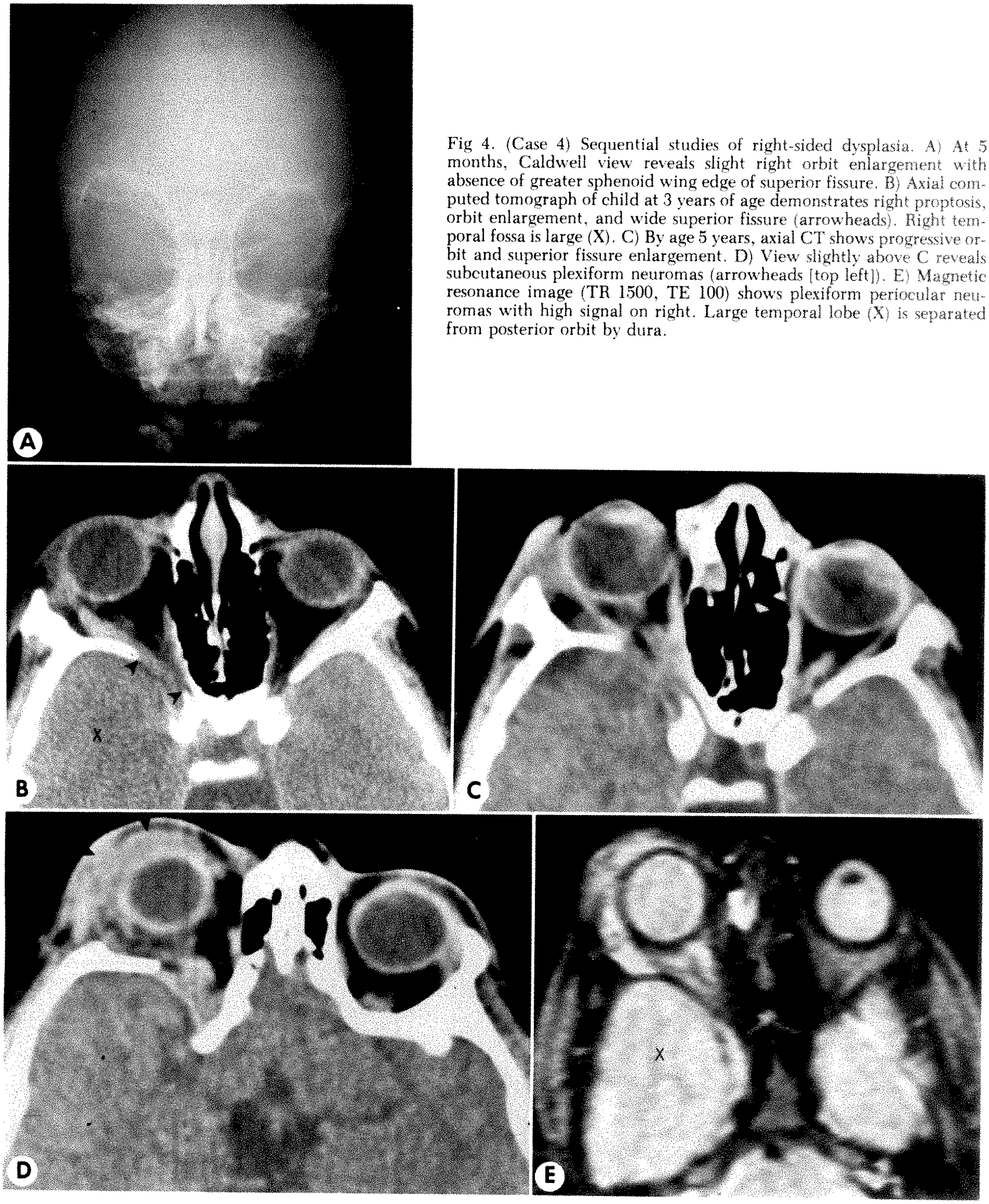

Fig 4. (Case 4) Sequential studies of right-sided dysplasia. A) At 5 months, Caldwell view reveals slight right orbit enlargement with absence of greater sphenoid wing edge of superior fissure. B) Axial computed tomograph of child at 3 years of age demonstrates right proptosis, orbit enlargement, and wide superior fissure (arrowheads). Right temporal fossa is large (X). C) By age 5 years, axial CT shows progressive orbit and superior fissure enlargement. D) View slightly above C reveals subcutaneous plexiform neuromas (arrowheads [top left]). E) Magnetic resonance image (TR 1500, TE 100) shows plexiform periocular neuromas with high signal on right. Large temporal lobe (X) is separated from posterior orbit by dura.

represent plexiform neuromas along the superior or orbital nerves in Fig 3B. The right ethmoid sinus is slightly decreased in size compared with the left side. Subcutaneous plexiform neuromas thicken the right upper eyelid and lesser temporal fossa in Fig 3C. This view also demonstrates enlargement of the right optic canal. No optic chiasm change was present in this examination.

Case 4. A 5-year-old boy had oculocutaneous albinism. A plain Caldwell view at 5 months of age, following a fall, shows slight enlargement of the right orbit and absence of the greater sphenoid wing (Fig 4A). Slight downward displacement of the right orbital floor is present, and the accompanying lesser sphenoid wing is elevated.

Proptosis of the right eye had appeared by 8 months of age. A CT taken at 3 years of age (Fig 4B) shows enlargement of the right temporal fossa, a large superior fissure, and elevation of the lesser sphenoid wing. Thickened soft tissue spans the su-

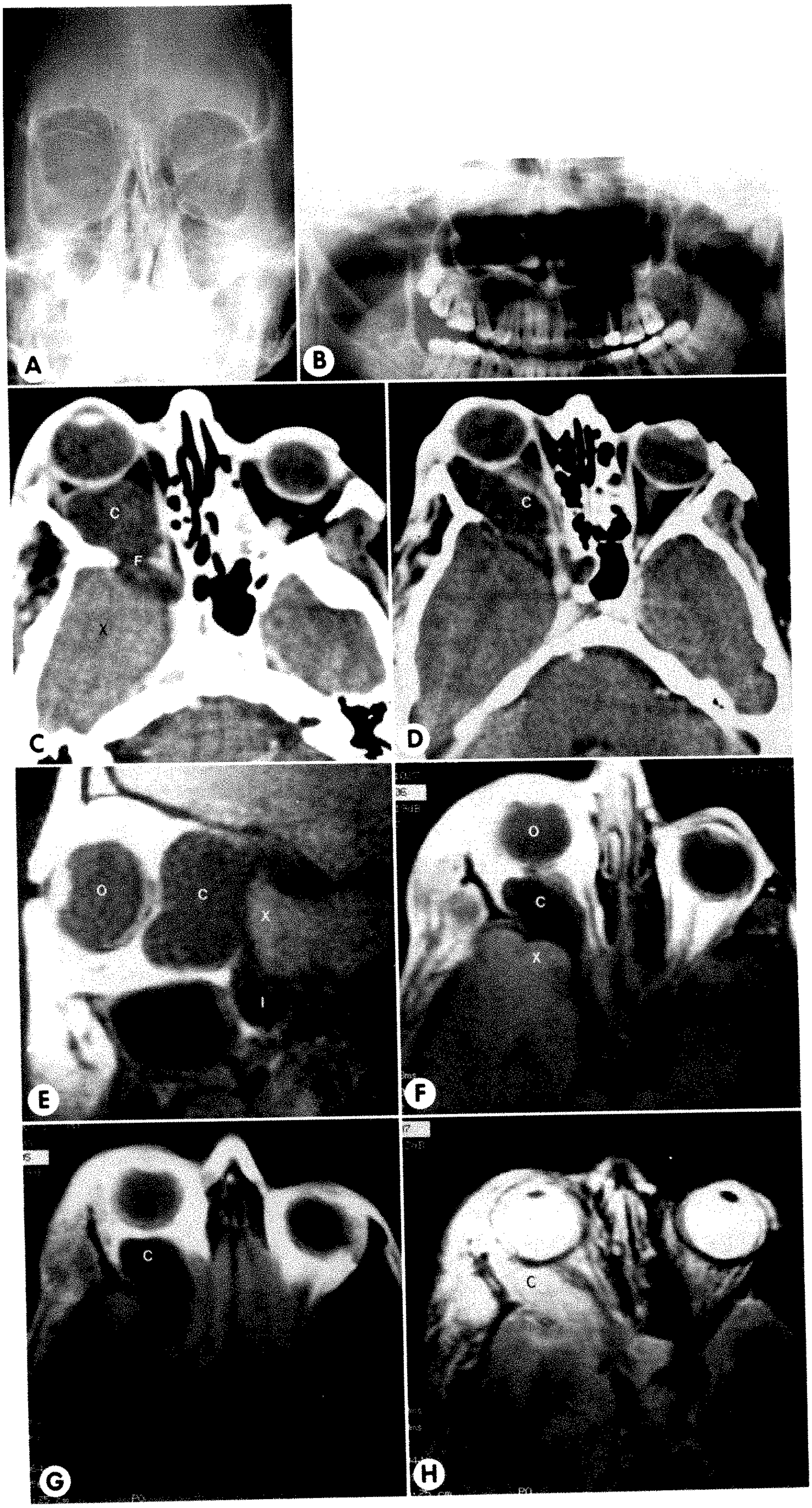

Fig 5. (Case 5) Right dysplasia with meningocele. A) Caldwell view with right orbit enlargement, large superior fissure, and elevated lesser wing. B) Pantomograph confirms small right maxilla with abnormal alveolar elevation and large neuroma thinning right mandible. C) Low axial computed tomograph shows proptosis produced by cystic mass in muscle cone (C). Large superior fissure (F) and temporal lobe (X) are evident. D) Higher axial CT shows cyst (C) displacing optic nerve medially. E) Sagittal T1 magnetic resonance image (TR 483, TE 20) defines ocular structures (O) displaced anteriorly by meningocele (C), which contains gyrus of temporal lobe (X). Small extension of cyst reaches inferiorly into inferior orbital fissure–pterygopalatine fissure area (I). F) Axial T1 MRI (TR 483, TE 20) better defines meningocele (C)–temporal lobe (X) relationship. O — orbit. G) Higher axial MRI (TR 483, TE 20) shows bone and dura separating upper cyst (C) and temporal lobe. H) Axial T2 MRI (TR 1,800, TE 100) shows high signal characteristic of CSF within meningocele (C).

perior fissure. A plexiform neuroma is present in the lacrimal gland area and displaces the globe away from the lateral orbital wall.

Proptosis gradually worsened during the next 2 years. A repeat CT taken at age 5 shows increase in size of the lateral orbit neuroma (Fig 4C). Superior fissure enlargement and temporal lobe enlargement persist. The optic canal is normal in size.

A higher CT cut in Fig 4D shows a diffuse plexiform neuroma development under the right upper lid. Elevation of the right lesser sphenoid wing and enlargement of the right temporal lobe are again evident. The brain tissue does not extend into the orbit and is separated from the orbit by a thick dural layer.

Magnetic resonance imaging also was performed at the same time as the last CT examination. The T1-weighted view in Fig 4E corresponds well to the CT study and again shows the orbit–temporal lobe separation.

Case 5. A 24-year-old woman had right-sided pulsatile exophthalmos. Figure 5A shows typical orbital and superior fissure enlargement. A pantomograph (Fig 5B) shows marked expansile change on the right producing a ribbonlike zygomatic arch, hypoplastic maxillary sinus, and profound thinning of the mandible, as well as enlargement of the proximal mandibular neural canal. The maxillary diminution disturbs the position of the maxillary alveolus. The CT results are similar to those in case 4 in respect to exophthalmos and the superior orbital fissure defect. The CT also shows a large meningocele filling the retrobulbar space. The large superior orbital fissure is evident in Fig 5C,D. The meningocele enters the orbit from the lateral side and displaces the optic nerve and vessels medially. The cavernous sinus is enlarged. The ethmoid sinus is compressed and narrow. An enlarged optic canal is present. Magnetic resonance T1 studies in sagittal and axial projections display the relation between ocular structures and the meningocele to best advantage. The temporal lobe lies in the middle fossa and does not extend through the large superior fissure.

DISCUSSION

Plain films, CT, and MRI all contribute to understanding the changes in sphenoid dysplasia. As indicated by our cases, plain films allow definitive diagnosis of the condition. Orbit enlargement at the expense in size of the ethmoid and maxillary sinuses, as well as superior orbit fissure enlargement and elevation, was present in each of our cases. This represents the dysplastic portion of the process.

Plain films also reflect the changes produced by the neurofibroma masses as well. Extrinsic compression by the neurofibromas produces distortion and thinning of the zygomatic arch and adjacent glenoid fossa. Mandible involvement results in a deep intercondylar notch, thinning of the vertical ramus, and enlargement of the mandibular neural canal proximally. Both the dysplastic and acquired portions of the disease are shown by plain films and have been described previously.[5,7]

Both CT and MRI reveal other parts of the process not directly evident on plain films. While ultrasound examination has been used to display the ocular and retrobulbar changes in this process, ultrasound does not adequately reveal the nature of the retrobulbar and middle fossa abnormalities. Also, CT and MRI give the examiner a better idea of the size and extent of the plexiform neuroma masses present.

The chief advantage offered by CT and MRI is the evaluation of the temporal lobe in sphenoid dysplasia. As seen in Fig 4E, the superior fissure may be "guarded" by a band of dura, or conversely, a meningocele may project into the retrobulbar region, as in Fig 5E. Theoretically, the temporal lobe might project into the retrobulbar meningocele, but it did not in our patient. It is of interest that in both of our cases studied by MRI, there was an increased volume of the temporal lobe on the side of dysplasia as compared to the volume of the opposite temporal lobe.

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CORRELATION BETWEEN MASTOID PNEUMATIZATION AND POSITION OF THE LATERAL SINUS

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The distance between the lateral sinus and the external ear canal was measured in 148 patients (150 ears) with completely sclerotic (nonpneumatized) mastoids and in 75 healthy random control subjects (150 ears) with pneumatized mastoids. A highly significant difference ($p < .0001$) was found between the two groups, the mean distance (±SD) among patients being 7.8±1.7 mm, while among controls it was 13.5±2.8 mm. Moreover, a significant positive correlation ($p < .001$) was found within the pneumatized control group itself, between the sinus' distance and the degree of mastoid pneumatization. The results of this study may be interpreted by those who espouse environmental theories as denoting that infantile otitis media will determine the position of the lateral sinus. However, those who favor the genetic explanation may maintain that since the position of the sinus is established prenatally and involves organogenetically the shape of the skull, the final position is unlikely to be influenced by postnatal otitis media.

KEY WORDS — lateral sinus, pneumatized mastoid, sclerotic mastoid.

INTRODUCTION

The question of the factors that influence the extent of mastoid pneumatization, ie, the postinflammatory (environmental) influence versus a genetic factor, has been disputed for years.[1-3] In our previous study[4] we have shown a link between otosclerosis, a hereditary disease, and the size of mastoid pneumatization. Another avenue to approach this question could be found by correlating the degree of pneumatization with a well-defined anatomic structure in the temporal bone that is unlikely to be influenced by postnatal (inflammatory) events. Such a structure could be found in the lateral sinus, which on the one hand is the main posterior border of the mastoid process, and on the other is also part and parcel of the entire skull framework. While it is a common clinical observation that the distance of the lateral sinus from the external ear canal is relatively short in mastoids that are poorly pneumatized, measurements of this observation are so far missing. The purpose of this study was to quantify and to look for a correlation between the amount of mastoid pneumatization and the distance of the lateral sinus from the external ear canal.

MATERIAL

The extent of mastoid pneumatization and the posterior position of the lateral sinus were examined in two groups. Group 1 consisted of 150 randomized healthy ears of 75 volunteers having no history of ear disease. All 150 ears showed normal eardrums on microscopic otoscopy and produced a normal audiogram. Group 2 consisted of 150 ears of 148 patients with completely sclerotic mastoids, retrieved from a patient population suffering from either simple chronic otitis media (30 ears or 20%) or from cholesteatoma (120 ears or 80%). The problem of the other ear or symmetry of pneumatization in the presence of a sclerotic mastoid will be the subject of a separate communication.

The age range of the two groups was 18 to 70 years, ie, ages far beyond the final stage of pneumatization development.[5] The sex distribution was about equal in both groups, ie, 49:51 (M/F) for normals and 47:53 (M/F) for sclerotics.

METHODS

The position of the lateral sinus was defined as the shortest distance from its anterior border to the posterior border of the external auditory canal, as seen on radiographs taken in the Schüller lateral projection. The posterior border of the ear canal, the anterior border of the lateral sinus, and the outer limits of the air cell system were marked on the x-ray films and transferred to transparent millimetric paper. Measurements of the pneumatized areas were performed directly by computerized planimetry. A Hewlett Packard 9111-A digitizer, operated in conjunction with a Hewlett Packard 9817-H computer, was used as described in detail in our previous study.[4]

RESULTS

Distance of Lateral Sinus From Posterior Wall of External Ear Canal. In group 1, the mean distance ±SD measured for the 150 normal ears was 13.5±2.8 mm (range, 8 to 22 mm) (Fig 1A). In group 2, the mean distance±SD for the sclerotic mastoids was 7.8±1.7 mm (range, 7 to 11 mm) (Fig 1B). There is a 42% difference between the means of the two groups, which is statistically highly significant

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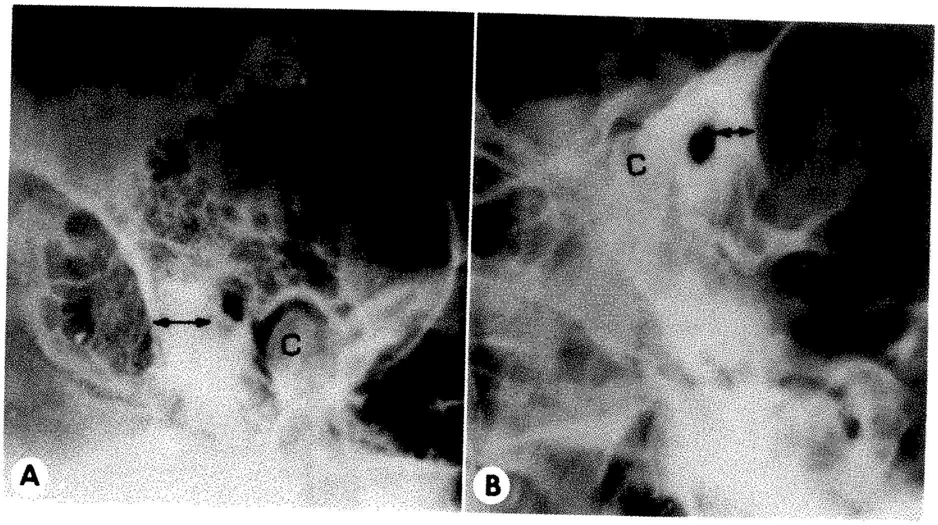

Fig 1. Radiographs showing distance of lateral sinus from external ear canal (arrows) in A) pneumatized mastoid and B) sclerotic mastoid. C — condyle of mandible.

(*t* test, $p < .0001$) and is also evident from the distribution of the distance within the two groups as demonstrated in Fig 2.

Correlation Between Extent of Mastoid Pneumatization and Distance of Lateral Sinus. When pneumatization was present, as it was in all the normal subjects, a correlation between the distance of the lateral sinus and the cross-sectional area of the mastoid pneumatization was looked for. Figure 3 presents this correlation, which is highly significant ($r = 0.474$, $p < .001$) and shows that the larger the pneumatization, the further the lateral sinus from the external ear canal. Because of the great symmetry of mastoid pneumatization in the healthy group, statistical evaluation was performed as follows: 1) taking all 150 ears into account, 2) taking only the 75 right ears, and 3) taking only the 75 left ears. No differences were found among these groups.

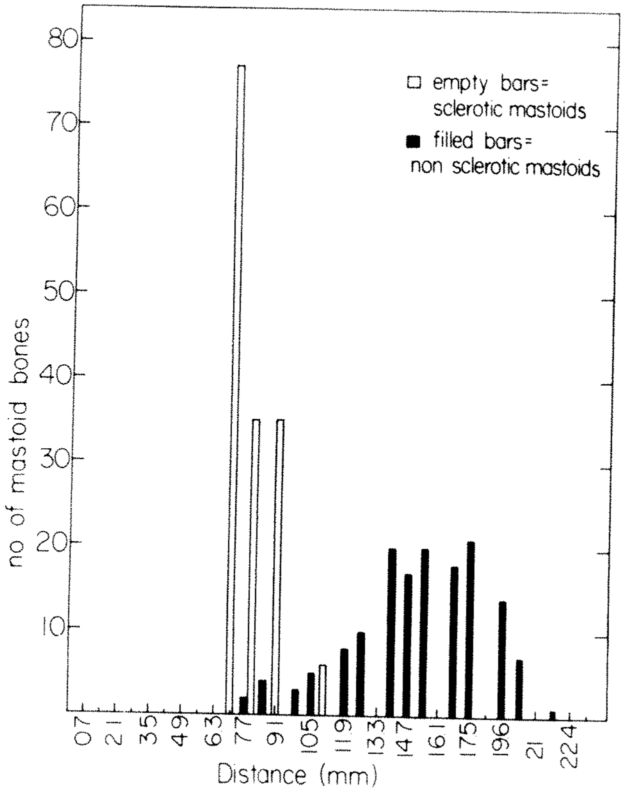

Fig 2. Distribution of distance of lateral sinus in normally pneumatized mastoids and sclerotic mastoids.

DISCUSSION

The present study confirms that the lateral sinus does not traverse the mastoid process in a fixed position. The variable course of the lateral sinus has been recognized previously by several authors.[6] Meltzer[7] as well as Tumarkin[8] studied in great detail the interrelationship between pneumatization and the lateral sinus from a surgical point of view. While no measurements as to the relationship of pneumatization to the position of the lateral sinus have been reported previously, most experienced otologists[9] gained the surgical impression that reduced pneumatization is related to a lateral sinus that lies far "forward," ie, close to the posterior wall of the external auditory canal. Virapongse et al,[10] who actually studied the relationship of the pneumatization to Korners' septum, could not find any correlation between these features.

Our present study adds two quantitative findings: 1) the existence of a significant relationship between the degree of mastoid pneumatization, in pneumatized mastoids, and the distance of the lateral sinus from the posterior border of the external ear canal; and 2) a consistent significant difference between nonpneumatized (sclerotic) mastoids on the one hand and pneumatized mastoids on the other, regarding the distance of the lateral sinus from the posterior border of the external ear canal.

As pointed out in the Introduction, the environmental versus the genetic influence on the size of the mastoid pneumatization has been disputed for years — proponents of environmental theories being usually in the majority.[1-3] The results of the present

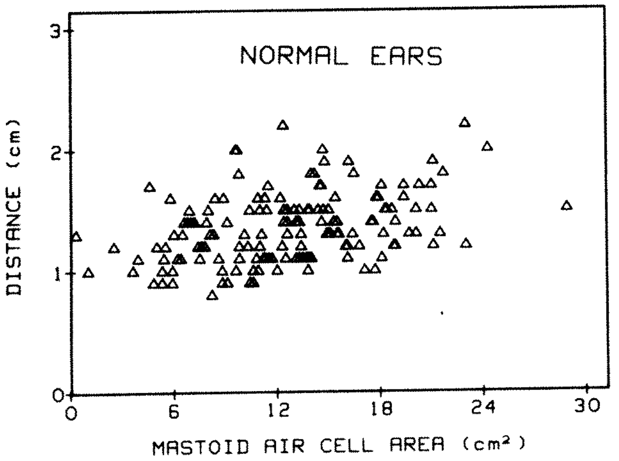

Fig 3. Correlation between distance of lateral sinus and cross-sectional area of pneumatized mastoids.

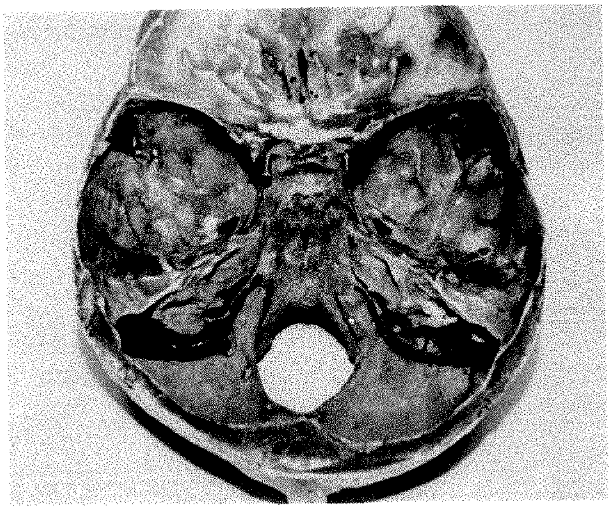

Fig 4. Base of skull from above showing lateral sinus (painted dark) as one of main structures traversing base of skull.

study can be interpreted by either school as proving its point. The environmentalists may see in early middle ear inflammatory disease a potent enough force to inhibit the development of the mastoid pneumatization and thereby to influence the position and place of the sigmoid sinus. The other school may, however, maintain that the sigmoid sinus is an organ whose structure is too big to be influenced by postnatal factors such as an inflammation — which usually occurs after the position of the major body already has been determined.

While the mastoid air cell system develops only after birth, the lateral sinus develops from the primary head veins, whose position in the temporal bone already is established by the seventh week of embryonal life.[11,12] Furthermore, should any postnatal events such as otitis in childhood be considered to affect the position of the lateral sinus, this would be tantamount to assuming that such an inflammation will affect the shape of the skull at a relatively late stage, as the sinus is a major structure on which the shape of most other bony parts of the skull depends (Fig 4). An exception to this could be a situation in which an inflammation of the middle ear, during the second or third year, would alter only the course of the mastoid segment of the lateral sinus. However, this latter situation is probably not the case, as is seen from the smooth course (presenting no kinks) the entire lateral sinus runs, in sclerotic as well as in pneumatized mastoids (Fig 1).

Our previous study[4] showed a highly significant ($p<.0001$) link between otosclerosis — a genetic disorder — and the degree of pneumatization. If the findings of the present study are interpreted as evidence of a genetic influence on the degree of pneumatization, one should take into account a complex heterogenous situation. Otosclerosis is considered to be due to a simple mutant gene,[13] while the position of the lateral sinus probably is influenced by more than one gene, in accordance with the polygenetic theory of inheritance.[14]

It should be pointed out that while these findings possibly may support the notion that the degree of mastoid pneumatization also has a genetic basis, they do not exclude the possibility that postnatal events also may influence the pneumatization process and determine its final degree. It is interesting that in the dispute between the nature (genetic) and nurture (environment, ie, inflammation) schools the supporters of either opinion have not considered the possibility that the two are not mutually exclusive.

Our present study did not include a possible intermediate group, the so-called diploic mastoid, which might form a link between the pneumatized and sclerotic mastoids whereby genetic determinants and postnatal influences might play a role concomitantly. This will be the subject of a separate communication.

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FIFTH INTERNATIONAL SYMPOSIUM RECENT ADVANCES IN OTITIS MEDIA

The Fifth International Symposium on Recent Advances in Otitis Media will be held May 20-23, 1991, at the Sheraton Bal Harbour in Bal Harbour, Florida. For further information, contact David J. Lim, MD, 4331 University Hospitals Clinic, 456 W Tenth Avenue, Columbus, OH 43210; Phone: (614) 293-8103; Fax: (614) 293-5506.

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CALL FOR POSTER ABSTRACTS GENETICS OF HEARING IMPAIRMENT SYMPOSIUM

The Genetics of Hearing Impairment Symposium will be held September 24-26, 1990, in New York City. Abstracts for posters are solicited in genetic determinates of normal hearing, gene mapping, registries, carrier features, animal models, developmental studies, transgenetic models, genetic susceptibility, and other aspects of the genetics of hearing impairment. Abstracts for posters are due May 1, 1990, and should not exceed 300 words. Extended abstracts for posters will be required for publication. Send abstracts for posters to Robert J. Ruben, MD, Chairman, Department of Otolaryngology, Montefiore Medical Center, 111 East 210th Street, VCA 4, Bronx, NY 10467-2490; (212) 734-5368.

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ANCIENT TEMPORAL BONE OSTEOPATHOLOGY

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Few isolated specimens or series of temporal bone abnormalities from antiquity are reported from North America. Infections were in the past and are today the most common otologic problems. Differentiating infectious disease residua from other causes of osteopathology has proven difficult for some not conversant with disease pathophysiology. During clinical experience spanning five decades and research involving several thousand aboriginal skeletons, data relating to temporal bone disease were accumulated. As a didactic exercise, findings in 18 illustrative temporal bones encountered during research are presented and discussed briefly.

KEY WORDS — mastoiditis, otitis media, paleopathology.

INTRODUCTION

Reports relating to abnormal temporal bones in ancient American skeletons have emphasized the effect of inflammatory disease upon the mastoid portion. These studies provided valuable information regarding the antiquity of infectious disease in the Americas.[1-7] However, in the experience of one of the authors (J.B.G.), students have difficulty interpreting and differentiating residua of infections from other osteopathologic findings in old skulls. Part of the problem is that with modern health care techniques in clinical medicine, untreated acute suppurative mastoid disease is infrequent, and clinicians rarely follow its course to spontaneous completion.

Today, "otitis media (OM) is the most common illness for which children receive medical care in the United States."[8] However, in the past 50 years mortality from otitis media has decreased markedly, and permanent damage to the ear structures is much less frequent. Better nutrition and socioeconomic conditions, education, improved health care, and antimicrobial drugs all have contributed to the decrease in the disease's severity.[9]

Before the advent of antimicrobial drugs, untreated otitis media subsided spontaneously or spread from the middle ear into the temporal bone, often leading to complications or death. If middle ear infections were virulent, or host response was lacking, temporal bone osteomyelitis was a frequent complication, often culminating in an abscess. Characteristically, abscesses penetrated the lateral cortex where it was weakest and often presented in the region of the suprameatal triangle (Fig 1[10]). If the infection subsided spontaneously or was treated surgically, a defect remained in the mastoid lateral surface where the cortex was perforated.

Vogel[11] discussed botanical treatment of ear infections in the Americas with *Nicotiana* spp (tobacco), *Achillea millefolium* L. (yarrow), *Asarum arifolium* (wild ginger), *Rhus typhina* (sumach), *Iris*

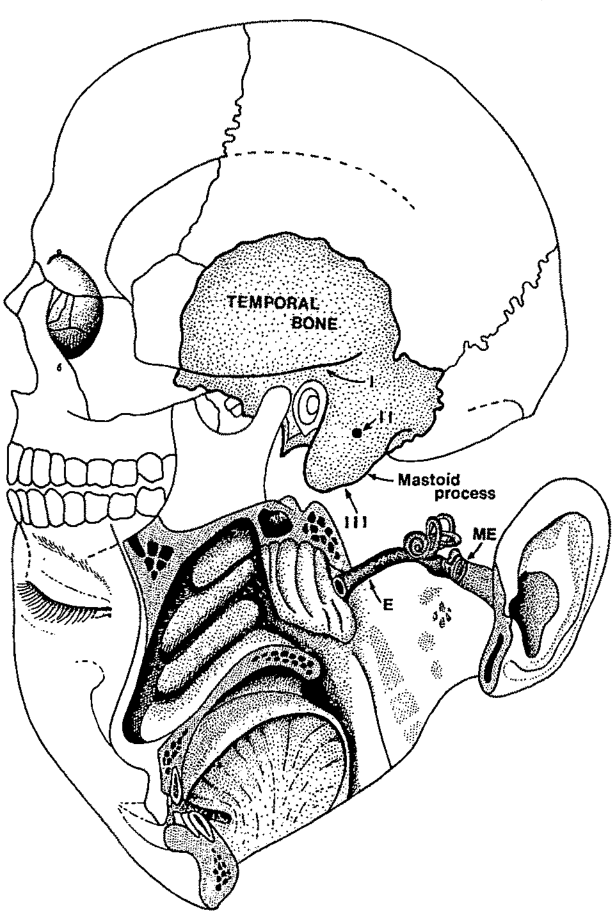

Fig 1. Adapted from Pfizer Spectrum. Upper) Common mastoid abscess external drainage points. I — suprameatal triangle overlying antrum (space) connecting middle ear and mastoid; II — emissary vein foramen; III — mastoid tip cells. (Adapted from Jackson and Jackson.[10]) Lower) Schematic anatomy of nose, pharynx, and ear complex. E — eustachian tube, ME — middle ear.

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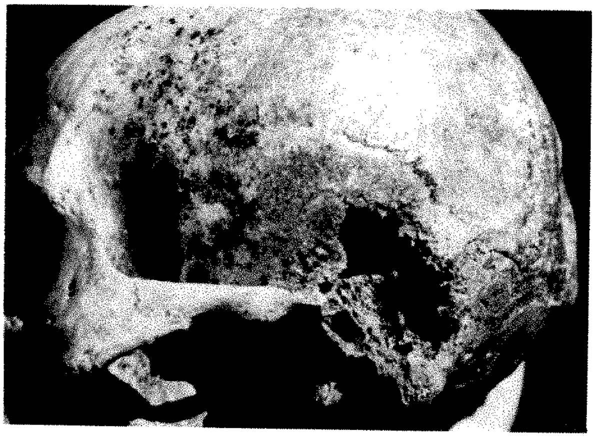

Fig 2. (Specimen 1) Extensive osteolytic defect in left temporal bone with no evidence of repair, interpreted as acute osteomyelitis and mastoid abscess, probably fatal. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

versicolor L. (blue flag), *Humulus americanus* Nutt. (hops), *Datura* spp (jimson weed), *Capsicum annuum* L. (cayenne pepper), and *Populus* spp (poplar or aspen). Except for tobacco, which was blown as smoke into the ear, the plants were used in salves or infusions.

Otitis media influences mastoid development, especially between birth and 4 years of age. Tremble[12] reported that a well-developed, uniform mastoid air cell pattern (pneumatic type) suggests that the temporal bone pneumatization process was not affected during development, or if it was involved by infection, it shows no residua thereof. Infectious middle ear disease early in life can retard pneumatization, with the result that the mastoid contained marrow bone (diploic type). Mixed pneumatization suggests that something occurred during mastoid development to interrupt normal growth patterns. Sclerotic mastoids, characterized by eburnated, dense bone and loss of the usual porous structure, indicate bouts of severe acute infection. Sclerotic change often accompanies chronic middle ear or mastoid disease.

Mastoid developmental status also affects the response to invading microorganisms. A disturbed mastoid development pattern correlates strongly with subsequent increased frequency of middle ear disease.[13] Thus, in old skulls changes in temporal bone cut sections or radiographs may be a rough indicator of infectious temporal bone disease during life.

Other abnormalities in temporal bones to be differentiated from residua of infection include congenital or developmental anomalies, neoplasms, and disturbances resulting from metabolic disease(s). To help future investigators, examples of temporal bone abnormalities we have seen during research are presented and discussed; interpretations are based on clinical experience in otology that spans the preantimicrobial and postantimicrobial eras.

MATERIALS AND METHODS

Eighteen exemplary temporal bone specimens encountered during our research are presented, including several encountered by others during research and submitted to one of us (J.B.G.) for evaluation. Each specimen was examined grossly and with an operating microscope, and when indicated, radiographic and other studies were performed. If a specimen's interpretation was equivocal, indicating the need for another opinion, it was referred appropriately for definitive expert analysis. The total specimen group came from diverse North American sites, cultures, and time frames that include the following.

1. Specimen 1 (Fig 2). 39WW1, Mobridge site, SD. Arikara. AD 1650-1750.
2. Specimen 2 (Fig 3). 39WW2, Larson site, SD. Arikara. AD 1750-1785.
3. Specimen 3 (Fig 4). 39WW7, Swan Creek site, SD. Arikara. AD 1650-1725.
4. Specimen 4 (Fig 5). W. H. Over Museum, Uni-

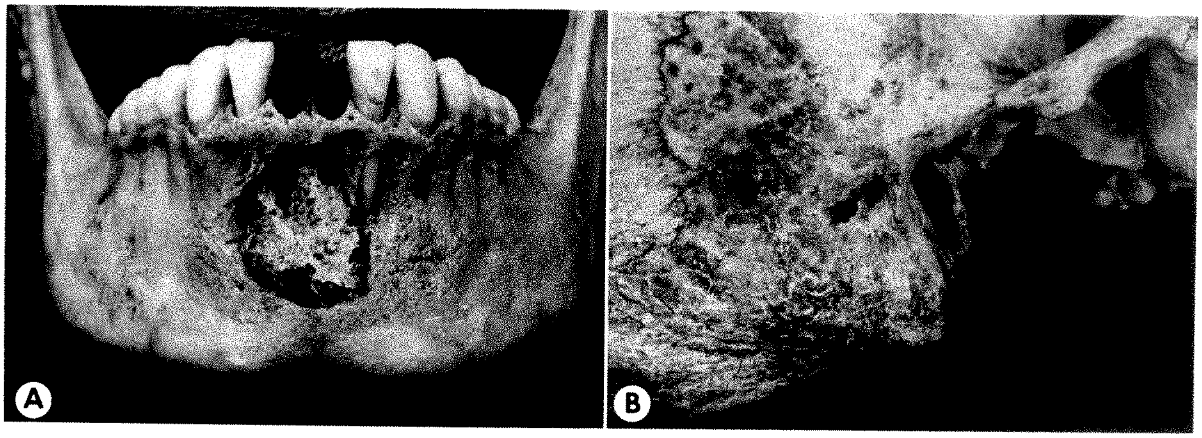

Fig 3. (Specimen 2) Acute osteomyelitis involving dental and ear structures, probably originating from oral cavity sepsis. A) Mandible. B) Mastoid. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

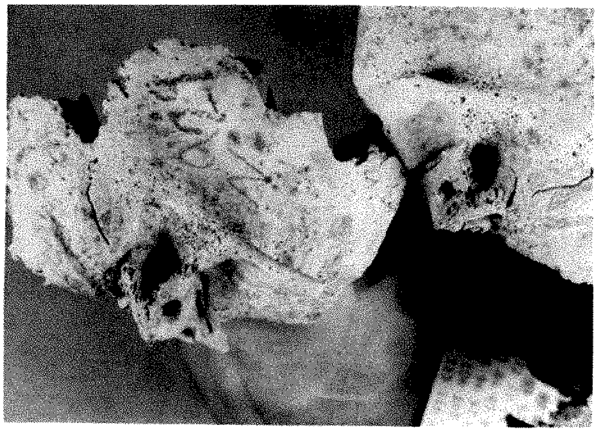

Fig 4. (Specimen 3) Temporal bones with poor mastoid development and punctate osteolytic defects in suprameatal triangle area. Orbital cribra were present. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

versity of South Dakota. Arikara; unknown culture and race.

5. Specimen 5 (Fig 6). 4MNT391, Saunders site, Monterey, Calif. 4,000-3,200 BP.
6. Specimen 6 (Fig 7). 243 376, Smithsonian Institution. Sioux.
7. Specimen 7 (Fig 8). University of Maine Museum, Gorham. Indian skull from Haiti, circa AD 1492.
8. Specimen 8 (Fig 9). 39BF11, Crow Creek site, SD. Proto-Arikara. AD 1350 ± 50 years.
9. Specimen 9. SIS6-F15-112, Gyftakis, St Ignace, Mich. Middle Woodland. AD 170 ± 80 years.
10. Specimen 10 (Fig 10). Tucson Presidio, Campos Santos Cemetery, Ariz. Spanish, circa AD 1776.
11. Specimen 11 (Fig 11). 42CA73, Cache County, Utah. Probable Shoshone, late prehistoric.
12. Specimen 12 (Fig 12). 39BF11, Crow Creek site, SD. Proto-Arikara. AD 1350 ± 50 years.
13. Specimen 13 (Fig 13). 40MR6, Toqua site, Tenn. Middle Mississipian. AD 1350-1650.
14. Specimen 14 (Fig 14A). North Dakota Historical Society Museum, Bismarck, No. 7653. Possible Mandan.
15. Specimen 15 (Fig 14B). 39C09, Leavenworth site, SD. Arikara. AD 1800-1832.
16. Specimen 16 (Fig 14C). 39ST1, Cheyenne River site, SD. Arikara.
17. Specimen 17 (Fig 15). 39BF11, Crow Creek site, SD. Proto-Arikara. AD 1350 ± 50 years.
18. Specimen 18 (Fig 16). 39BF11, Crow Creek site, SD. Proto-Arikara. AD 1350 ± 50 years.

FINDINGS AND INTERPRETATIONS

RESIDUA OF TEMPORAL BONE INFLAMMATORY DISEASE

Acute Destructive Disease: Mastoiditis and Abscess Formation. Specimen 1 (Fig 2) is from a 40- to 45-year-old man. Dissolution of most of the left mastoid and contiguous temporal bone probably came from overwhelming infection; the right side was normal. Extensive osteolysis precluded radiographic diagnosis. The anatomic findings were interpreted as acute otitis media leading to mastoid osteomyelitis, abscess formation, and involvement of intracranial structures, which was probably the cause of death. The absence of other skeletal abnormality implicates disease in the craniofacial area.

Acute Penetrating Mastoiditis. Specimen 2 (Fig 3) is from a 20-year-old woman. The osteolytic defects in the mandible's midportion and the left temporal bone's suprameatal triangle are commensurate with acute osteomyelitis, originating in the oral cavity. The otic infection probably presented as a postauricular abscess. The active lesions indicate an ongoing process that contributed to the fatal outcome. Reactive bone on the temporal bone lateral surface superior to the external auditory canal suggests either previous mastoid disease or an early stage reparative response. Radiographs are not available.[14]

Acute Inflammatory Response, Temporal Bone Lateral Surface. Specimen 3 (Fig 4) is from a 4- to

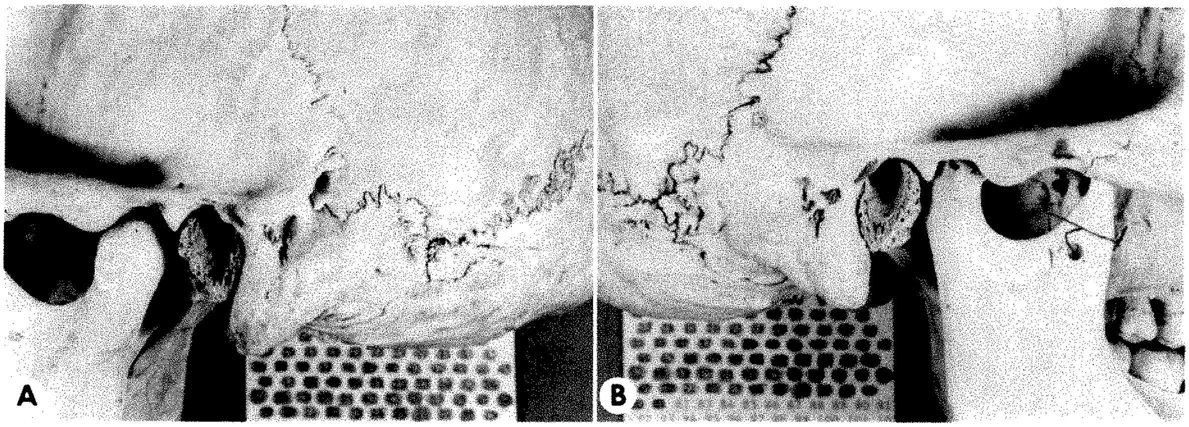

Fig 5. (Specimen 4) Bilateral penetrating defects in suprameatal triangle mastoid cortex, probably residua of previous infection. A) Left ear. B) Right ear. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

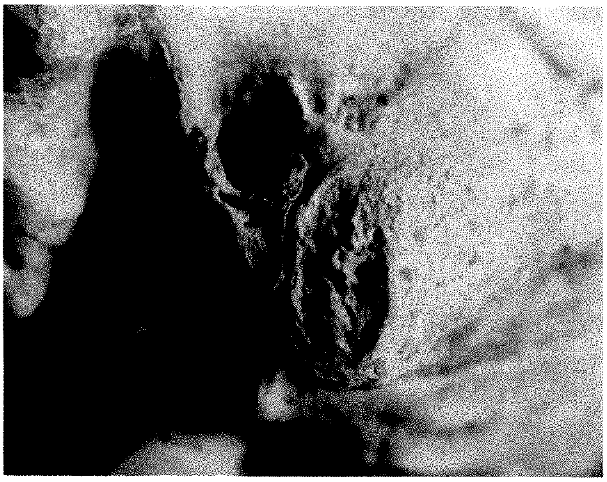

Fig 6. (Specimen 5) Cortical defects in mastoid tip cells and suprameatal triangle, interpreted as residua of previous infection (Bezold's abscess). (Specimen recovered by Robert Cartier, Archaeological Resource Management, San Jose, Calif.)

6-year-old child. The punctate cortical defects above both external auditory canals and in the suprameatal triangle suggest inflammation. The mastoids were underdeveloped. If these changes were of infectious origin, they are more typical of the response to outer ear infection (otitis externa) than of otitis media. Small orbital cribra were in this skull, suggesting as an additional consideration the possibility of a metabolic origin for the temporal bone defects.

Healed or Chronic Mastoiditis. Specimen 4 (Fig 5) is in the W. H. Over Museum, labeled "W. (Arkansau), Pierre, SD, (James Pollar, shot by vigilantes, Pierre, SD, 1881)." It is from a 30- to 35-year-old man. The multiple bilateral old suprameatal triangle mastoid cortex perforations with smooth edges and no obvious active disease are commensurate with previous infection. The subject could have had chronically draining postauricular sinuses during at least a part of his life. No radiographs are available.

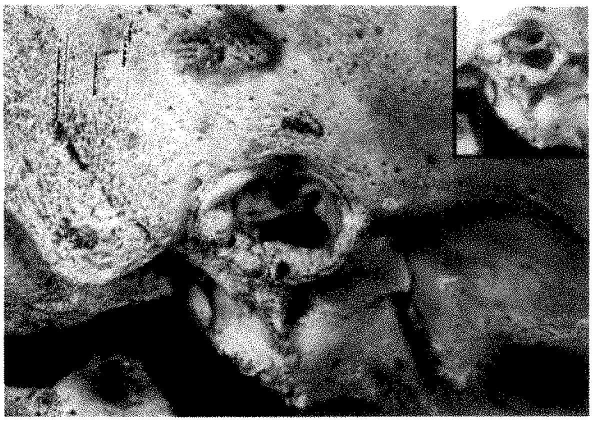

Fig 7. (Specimen 6) Invaginated healed defect superior to right suprameatal triangle. Radiograph shows microtia, malleolar tip, and anterior ligament fusion to tympanic ring. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

Specimen 5 (Fig 6) is from an adult with an oval, 13 x 10-mm quiescent defect in the left mastoid lateral cortex. Where the defect is deepest, the bone's surface is eroded 2 to 3 mm. Mastoid cells in the defect's depths are covered by thin bone. In addition there is a slightly invaginated defect in the suprameatal triangle. Radiographs were not diagnostic. These findings are interpreted as residua of an abscess (Bezold's) that exited through the mastoid tip cells, was walled off, was encapsulated, and finally became dormant.

Specimen 6 (Fig 7) from the Smithsonian Institution (No. 243 376), is from a Sioux child 1 to 2 years of age (no provenience). An invaginated healed defect superior to the right suprameatal triangle suggests the possibility of previous middle ear and mastoid disease. The opposite temporal bone was normal. Radiographs showed no pneumatization (diploic) on the right and partial pneumatization (mixed) on the left, indicating the effect of intravital infections. (See Congenital and Developmental Anomalies, below.)

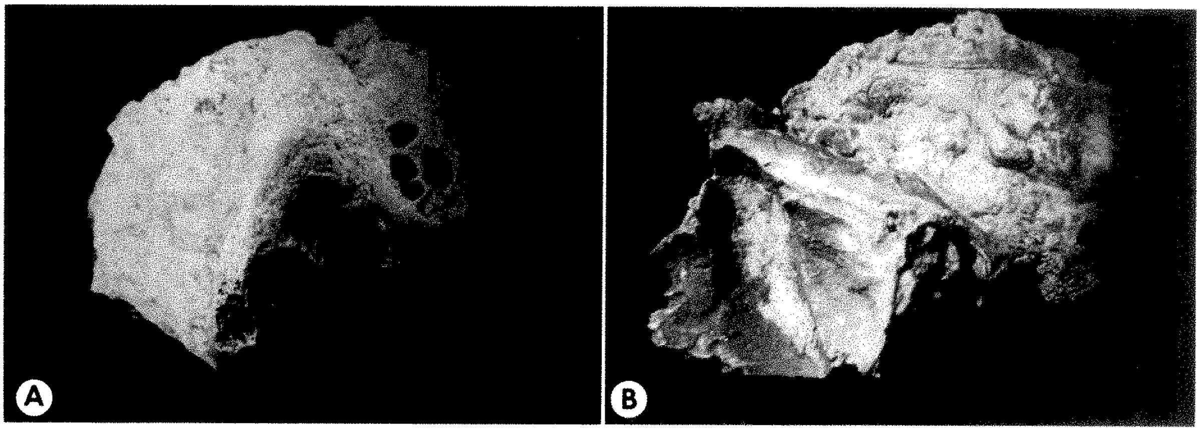

Fig 8. (Specimen 7) (Photographs courtesy of P. Provost.) A) Partially postmortem erosion on mastoid lateral surface. B) Nodularity on medial surface represents response to irritation, possibly protective meningitis.

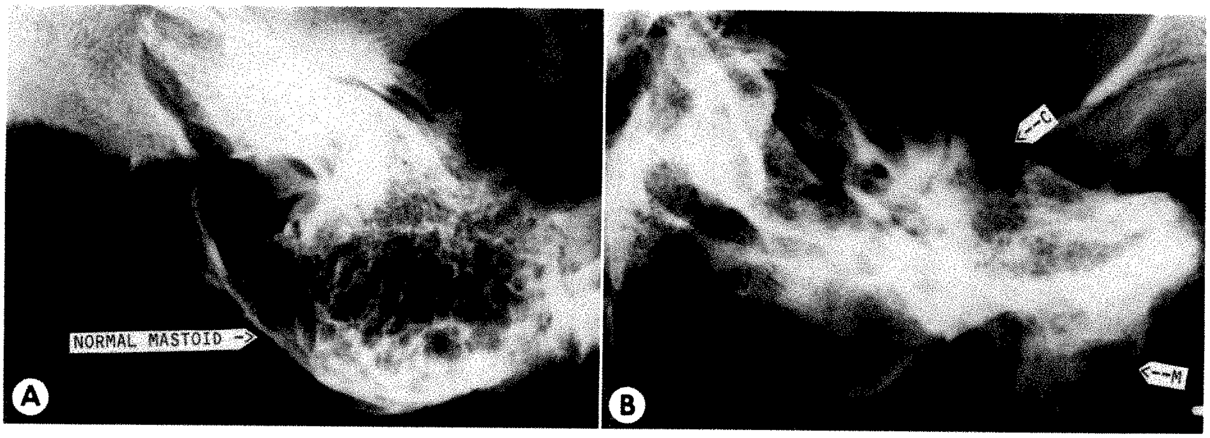

Fig 9. (Specimen 8) Stenvers (posteroanterior) radiographs of adult temporal bones. A) Normal air cell development (arrow). B) Mixed pneumatization (<--M) and defect suggesting cholesteatoma (<--C). (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

The cortical defects in specimens 4, 5, and 6 look old; the latter two appear inactive. Specimens such as these with evidence of healing suggest that in the distant past complicated ear infections existed, resolved spontaneously, and were not always lethal.

Chronic Inflammation With Complications. Specimen 7 (Fig 8), from an adult (Indian) in Haiti, is in the University of Maine Museum. The thin lateral cortex of the left mastoid has been partially exposed by soil erosion, but there is also evidence of previous mastoid disease with resolution. Irregular smooth new bone formation on the medial surface anterosuperior to the petrosquamosal suture suggests an irritative process during life, possibly protective meningitis (meningitis sympathica).[10] No radiographs or other skeletal components are available.

Specimen 8 (Fig 9), from an adult, shows a normal air cell pattern (Fig 9A) and mixed pneumatization and a defect interpreted as a cholesteatoma complicating chronic ear disease (Fig 9B). Although the defect is so located that meningitis and brain abscess are potential complications, the subject apparently was not seriously affected by this problem and perished in the Crow Creek massacre (circa AD 1350). It is likely that hearing was reduced in the affected ear. The mixed type mastoid pneumatization provides evidence confirming the presence during life of long-term and/or repeated otitis media.

Specimen 9 was from a 25- to 30-year-old man. The specimen was referred to one of us (J.B.G.) for evaluation. Both mastoid lateral surfaces had inflammatory reaction in the suprameatal triangle and outer ear canal bone. A perforation in the right triangle posteriorly exposed the mastoid interior. Medial surface erosive changes on both temporal bones indicated intracranial extension of the process. Radiographs were compatible with previous inflammatory disease. The “clinical picture” demonstrated was that of chronic smoldering middle ear

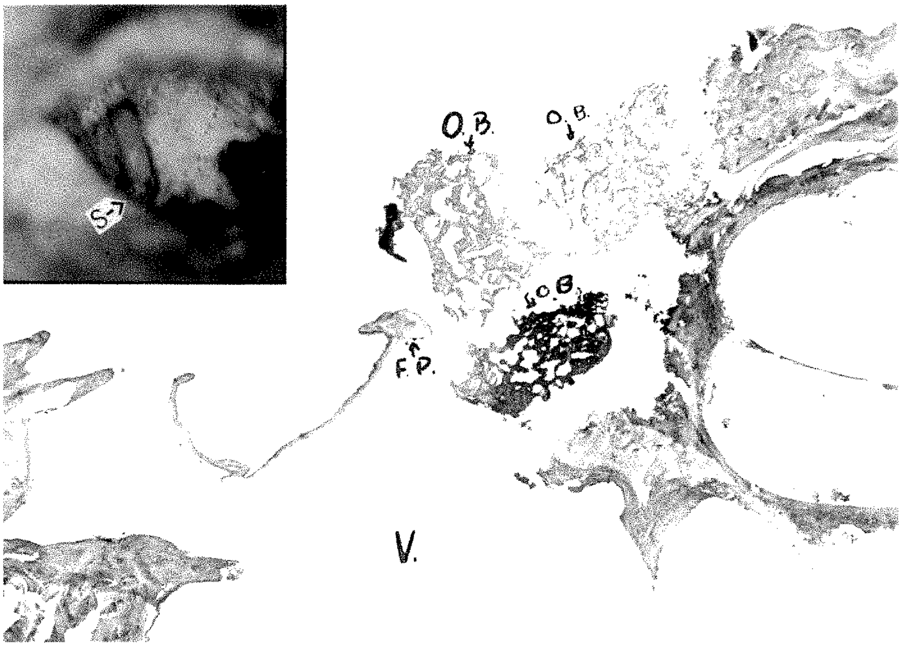

Fig 10. (Specimen 10) Histologic section of middle ear with stapes fixation (otosclerosis). (Specimen supplied by W. Birkby, Human Identification Laboratory, University of Arizona, Tucson.) F.P. — stapes footplate, O.B. — otosclerotic bone, V. — vestibule. Inset) Operating microscope view. S — stapes.

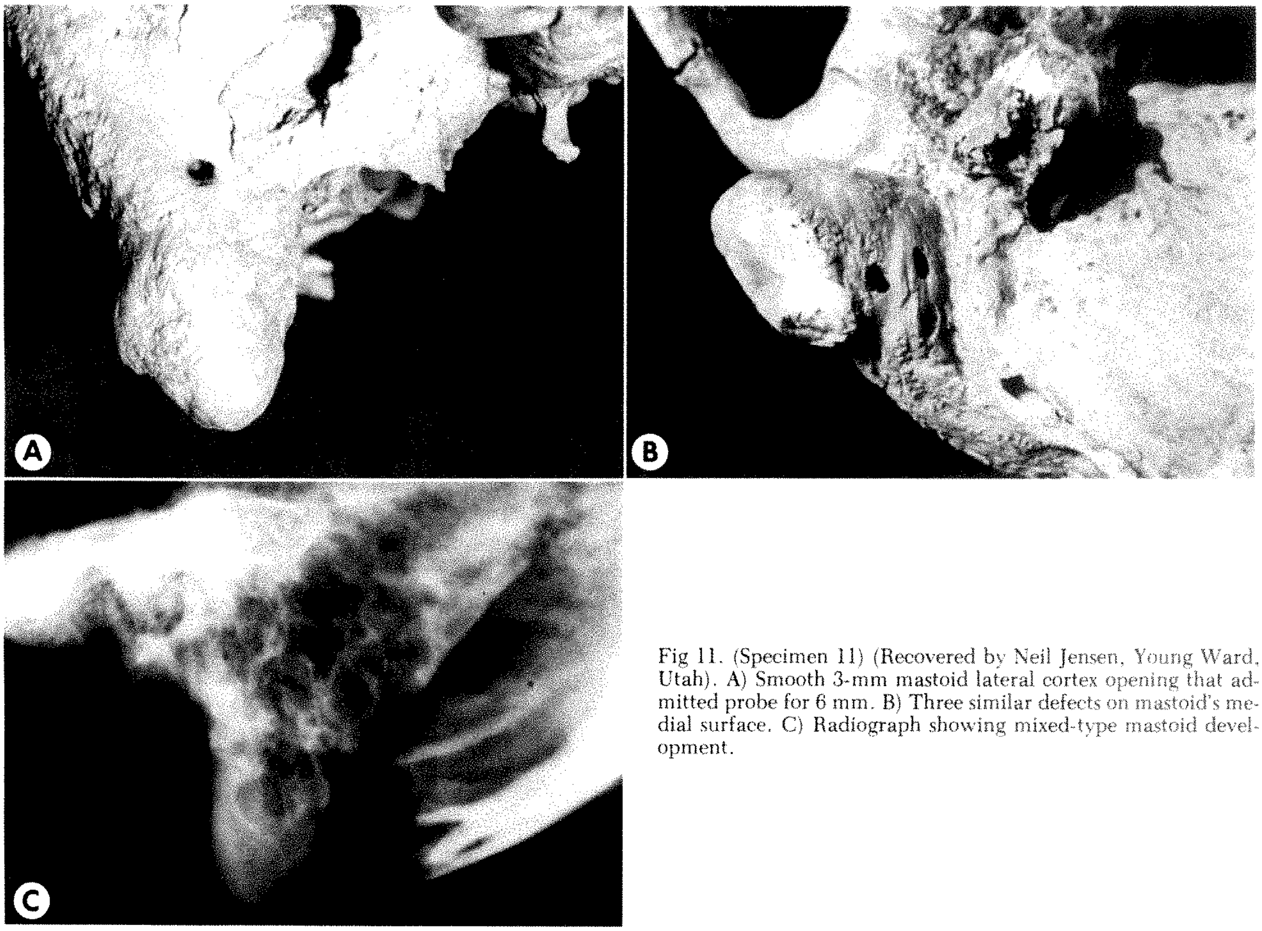

Fig 11. (Specimen 11) (Recovered by Neil Jensen, Young Ward, Utah). A) Smooth 3-mm mastoid lateral cortex opening that admitted probe for 6 mm. B) Three similar defects on mastoid's medial surface. C) Radiograph showing mixed-type mastoid development.

and mastoid disease, indicated by cholesteatoma formation and intracranial extension. Secondary to intracranial disease, sigmoid sinus thrombosis (infected blood clot) and meningitis or brain abscess were potential causes of death[15] (personal communication, R. I. Sundick, Western Michigan University, Kalamazoo, 1988).

Radiographic studies have demonstrated convincing evidence of otitis media in antiquity in several areas of the world.[1,2,4,6,7,16,17]

Other Specific Bone Disease. Specimen 10 (Fig 10), from the Campos Santos Cemetery, is from a white, 40- to 50-year-old man. The operating microscope photograph (inset, Fig 10) shows the stapes footplate firmly immobilized in the oval window. Temporal bone tomograms demonstrate stapes fixation. In histologic sections abnormal bone is in the otic capsule and at the oval window edge. The anatomic, radiographic, and histologic demonstration of stapes footplate fixation and otic capsule involvement by abnormal bone confirm the presence of otosclerosis.

This hereditary disease affects 1/100 in the US general population, causes conduction type hearing loss, follows typical age and sex patterns, is primarily a disease of whites, and once was thought to be precipitated by middle ear infection. This specimen, discovered by Walter Birkby in 1970, was the first authenticated instance of otosclerosis with stapes footplate fixation reported in the literature of paleopathology.[18]

Congenital and Developmental Anomalies. Specimen 6 (Fig 7) shows a stenotic, congenitally small external ear canal in which there was smooth bony fusion of the malleolar manubrium to the tympanic ring in the usual plane of the tympanic membrane. This, and anterior-superior fusion of the anterior

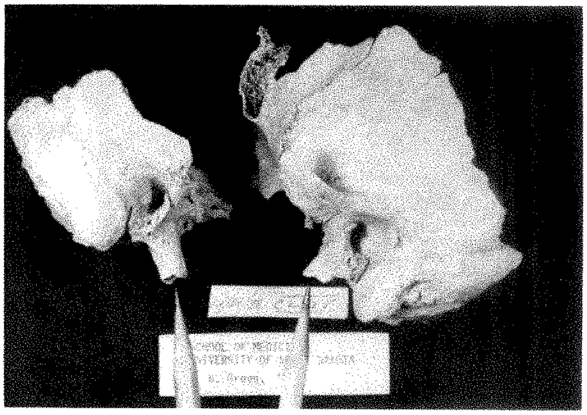

Fig 12. (Specimen 12) Bilateral thick styloid processes that are developmental anomalies. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

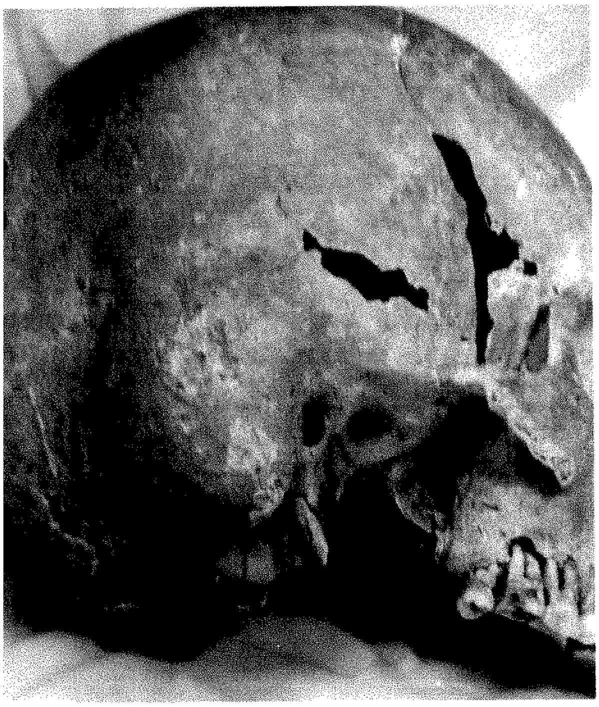

Fig 13. (Specimen 13) Large, invasive, grossly benign fibrous tissue tumor has replaced right mastoid and contiguous temporal bone. (Specimen excavated by A. Reed, University of Tennessee, Knoxville.)

nalleolar ligament, indicate congenital maldevelopment. No evidence was found of other congenital anomalies in available skeletal components.[19] (See Other Specific Bone Disease, above.)

Specimen 11 (Fig 11) is from a man in Cache County, Utah. In the right mastoid lateral cortex just inferior to the external auditory canal there is a round opening (3 mm) into the bone. Its edges are smooth and it appears to be old. The defect's lumen is directed posterosuperiorly and can be probed for 6 mm. Three similar holes are in the mastoid medial surface (Fig 11B). The left temporal bone was missing. Radiographs show mixed type pneumatization, but no other diagnostic features (Fig 11C). The defects are situated where emissary vein canals exist and are portals through which mastoid abscesses evacuate (Fig 1). Although the radiographs implicate previous otitis media, the gross appearance suggests a noninfectious cause.

On the basis of original research relating to venous and lymphatic drainage of the human basicranium, Parke[20] (and personal communication, 1988) concurred in the interpretation of these findings as anomalous emissary veins.

Specimen 12 (Fig 12) is a disarticulated specimen from Crow Creek, probably from a man. The styloid processes are extremely thick (7 mm; normal is 1 to 2 mm). Unaccompanied by other temporal bone abnormality, the thickness of the styloid processes is considered to be of developmental origin. The radiographs were not abnormal.

Tumor. Specimen 13 (Fig 13) is from a 39- to 44-year-old man. The entire mastoid portion and much of the right petrous apex are replaced by evenly spaced, anastomosing coarse-fiber bone tra-

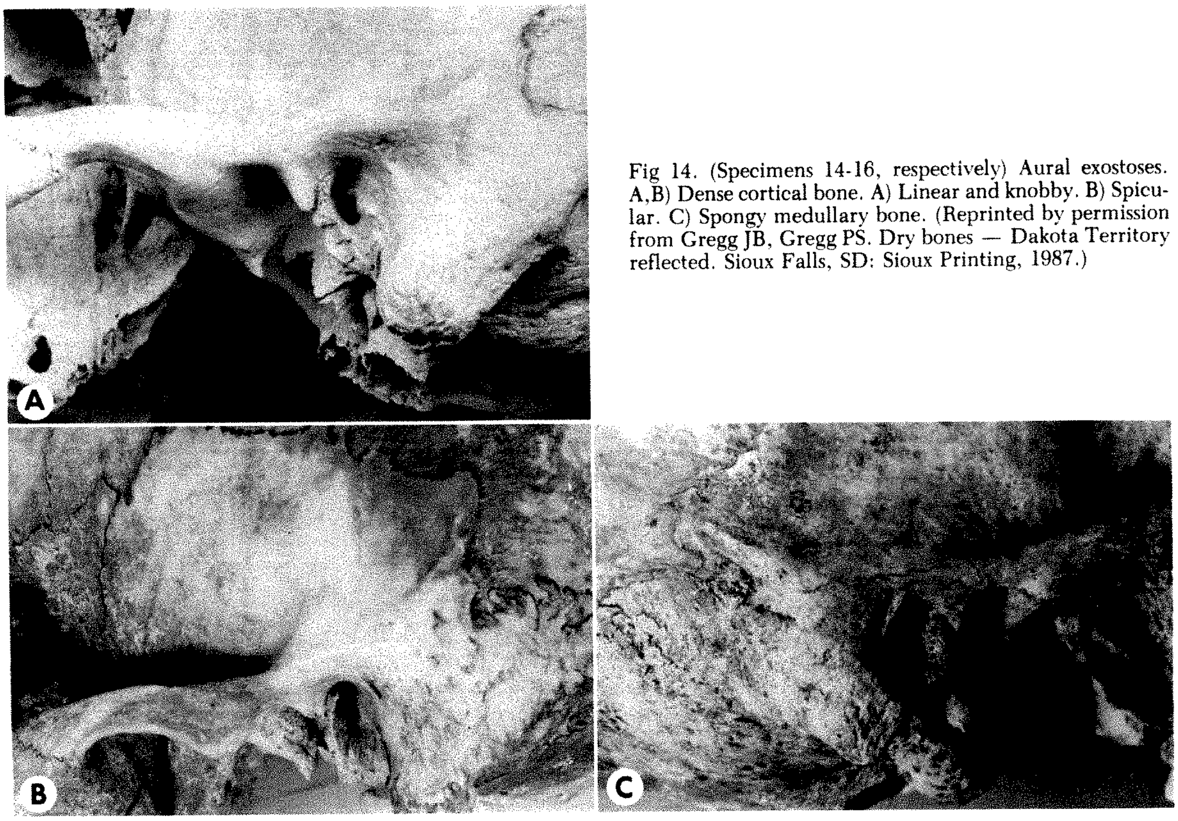

Fig 14. (Specimens 14-16, respectively) Aural exostoses. A,B) Dense cortical bone. A) Linear and knobby. B) Spicular. C) Spongy medullary bone. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

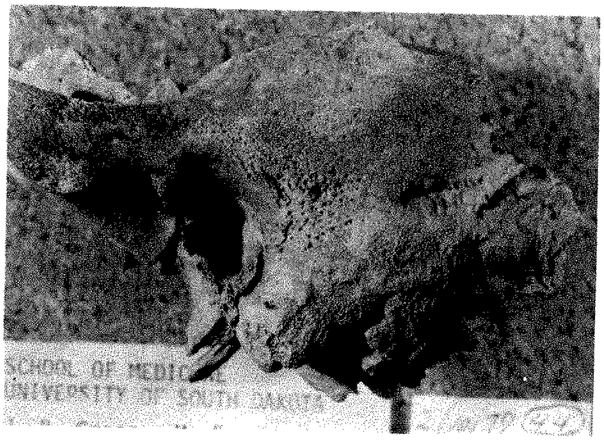

Fig 15. (Specimen 17) Temporal bone with abnormal surface markings of undetermined origin, probably not infectious. Organizing hematoma is possible. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

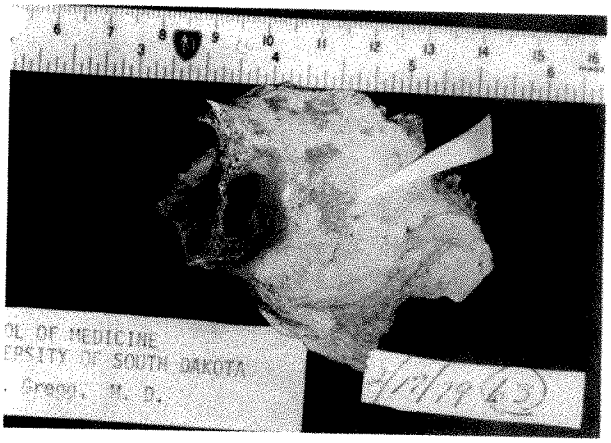

Fig 16. (Specimen 18) Temporal bone specimen similar to many other Crow Creek massacre bones. Surface is marked by firmly adherent substance that is probably calcifying subperiosteal hematoma. (Reprinted by permission from Gregg JB, Gregg PS. Dry bones — Dakota Territory reflected. Sioux Falls, SD: Sioux Printing, 1987.)

beculae. Radiographs showed mottled-appearing bone within which there was irregular destruction and new bone formation, but no demarcation or encapsulization. Findings on cut surface examination and radiography were interpreted as residua of benign intravital cortical and medullary bone replacement by fibrous tissue. Although only osseous structures remain, the findings are compatible with fibrous dysplasia. No other significant skeletal abnormality is evident.[21]

Specimen 14 (Fig 14A) (North Dakota Historical Society Museum) is from a 40- to 45-year-old man, specimen 15 (Fig 14B) is from a 30- to 35-year-old man, and specimen 16 (Fig 14C) is from a 25- to 30-year-old man. Benign tumors (exostosis, osteoma) arising from dense cortical bone appeared in about 5% of adult external auditory canals in three configurations: linear (Fig 14A), knobby (Fig 14A), and spicular (Fig 14B). A fourth type, which had its origin from medullary bone (spongy; Fig 14C), was uncommon. Radiographs of Fig 14C show no other abnormality.

Chronic irritation to ear canals, such as that from swimming in cold water, has been cited as causative for exostoses.[22-24]

Metabolic Disease. Specimen 17 (Fig 15) is from an adult, probably a man. The inflammatory external surface markings of undetermined origin on this Crow Creek massacre victim's temporal bone proved enigmatic. They are not characteristic of middle ear disease, but could have come from a deep space infection with external otitis or could have accompanied severe soft tissue trauma. Although an infectious origin is possible, in light of much other evidence of scurvy at Crow Creek,[25] an organizing hematoma due to scurvy must be considered. No similar change was found in other skeletons or in the available literature (see specimen 3).

Specimen 18 (Fig 16) is from a child of unknown age. An unusual dark-colored porous substance is intimately adherent to the temporal bone lateral surface. Similar material was on many different bones in the Crow Creek massacre victims' communal burial. On some bones these deposits were closely associated with calcifying subperiosteal hematomas. Similar markings were not seen in other skeletons and have not been illustrated in the available literature. These were interpreted as early organizing subperiosteal hematomata, probably complicating scurvy.

SUMMARY

Exemplary temporal bone specimens from several locations in North America that have been evaluated during the past 25 years have been illustrated and discussed briefly. Determination of the pathogenesis of some findings required considerable investigation into the anatomy and pathophysiology potentially instrumental in the development of temporal bone abnormalities.

The antiquity of infectious temporal bone disease has been established in several areas of the world. However, for investigators unfamiliar with the clinical course of diseases and for those having limited or no experience with preantimicrobial ear infections, interpretation of abnormalities in old skulls can be perplexing.

Analysis of the left temporal bone of Kabwe man from Broken Hill Mine, Zambia, is an excellent example. Yearsley[26] described the abnormalities in detail and attributed the defect in the squama to an injury or a pus tract, and the mastoid findings to a Bezold's abscess. McKenzie and Brothwell[27] disagreed with the diagnosis of Bezold's abscess. Price and Molleson[28] interpreted the small round defect (approximately 8 mm) in the Kabwe temporal bone radiographs as possibly the result of a benign tumor. Obviously, conflicting opinions evolved from the different studies of this single ancient specimen.

Although many mastoid alterations in old skulls are attributable to infectious disease, other processes always must be considered as differential possibilities. Thorough knowledge of the pathophysiology of various disease processes and emphasis upon the clinical aspects of temporal bone disease will facilitate interpretation of unusual findings.

ACKNOWLEDGMENTS — We are grateful to Pfizer Pharmaceuticals and Harry Wiener, MD, Director of Professional Services, for permission to use Fig 1, which was adapted by Ellen Parker; Pierre Provost, Westwood, Mass, for specimen 7; Robert Hull and Robert Sundick, Kalamazoo, Mich, for specimen 9; Ben Senturia (deceased), St Louis, Mo, for tomograms; Harold Schuknecht, Boston, Mass, for histologic sections, photomicrographs, and interpretation of specimen 10; and Lent Johnson, Orthopedic Surgery Branch, Armed Forces Institute of Pathology, Washington, DC, for interpretation of specimen 13. Specimen 13 was recovered under National Park Service contracts CX-5000-5-0213 and CX-5880-7-0055, Heritage Conservation and Recreation Service contracts C-5560(78) and C-5944(79), and Tennessee Valley Authority contracts TV42163A and TV48117. The Crow Creek skeletal material was recovered under contract with the US Army Corps of Engineers, Omaha District, purchase order No. DACW 45-78-C-0018.

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DECREASE IN XENON CLEARANCE DURING RESPONSE TO COLD, DRY AIR: PROBLEMS OF INTERPRETATION

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In order to increase our understanding of the nasal response to cold, dry air (CDA), we studied changes in xenon clearance as an indicator of nasal blood flow. Eight individuals previously shown to respond to CDA had measurements of xenon clearance made in the left inferior turbinate before, during, and after a 15-minute exposure to either CDA ($-7°C$ to $0°C$, $<10\%$ relative humidity) or room air. The half-life in seconds for xenon clearance on the day when CDA was inhaled was 56 ± 6, 41 ± 5, and 110 ± 31, before, during, and 10 minutes after challenge, respectively. On the control day, with subjects breathing room air, the equivalent measurements of half-life in seconds were 54 ± 8, 41 ± 6, and 42 ± 4, respectively. Xenon clearance was prolonged significantly ($p < .01$) after exposure to CDA during the clinical response. The interpretation of the change in xenon clearance as an indicator of nasal blood flow is discussed.

KEY WORDS — cold dry air, nasal blood flow, xenon clearance.

INTRODUCTION

The regulation of blood flow during illness and environmental stresses is poorly understood. Cauna and Hinderer[1] stated that nasal patency was regulated by blood volume; nasal air temperature, by blood flow through the superficial vascular plexus; and humidification, by the control of fluid movement through the fenestrated capillaries near the epithelial surface and surrounding the submucosal glands. Their beliefs were based on anatomic observations rather than on physiologic measurements. Support for these concepts in vivo has been limited by the inability to apply techniques useful in the study of animals to humans.

We studied the nasal response to an environmental stimulus: cold, dry air (CDA). The inhalation of CDA causes nasal congestion.[2,3] Togias et al,[4,5] in an attempt to understand the pathophysiology of this response, noted that at least in the extremes, there are two groups of subjects: those who respond with nasal symptoms consisting of rhinorrhea and congestion, and those who do not. The group responding to nasal challenge with CDA releases histamine, prostaglandin D_2, and other mast cell–associated mediators during the clinical response, whereas nonresponders do not.[4,5] In recent investigations, the osmolality of nasal secretions increased in responders compared to nonresponders.[6] These observations led to the hypothesis that humidification of inspired air induces evaporative water loss. In some individuals, this loss exceeds the normal physiologic control mechanisms, causing a hyperosmolar milieu. Hyperosmolality then triggers mast cells to release or generate inflammatory mediators that not only increase fluid movement but also cause concomitant nasal symptoms. This hypothesis is supported by the observations that hyperosmolality triggers mast cells to release histamine in vitro and that nasal challenge with hyperosmolar solutions induces histamine release in vivo.[7,8] We anticipated that blood flow and its effect on humidification would be a major determinant in the response to CDA.

Bende et al,[9] Druce et al,[10] and Konno et al[11] all have developed methods to study blood flow in vivo in humans. Because of the relative simplicity of the xenon clearance method developed by Bende et al, we applied this technique to study nasal blood flow during inhalation of CDA. This report describes the changes in xenon clearance during inhalation of CDA and discusses the difficulties of equating xenon clearance with nasal blood flow.

METHODS

We performed a randomized crossover study comparing the rate of xenon clearance before, during, and after the inhalation of CDA with similarly timed measurements of clearance on another day when subjects breathed room air. Each laboratory visit was separated by at least 1 week to minimize any potential influence of either the measurement or the challenge on subsequent observations.

Nine subjects participated in the study. Each subject previously showed a positive response to nasal challenge with CDA, a positive response being de-

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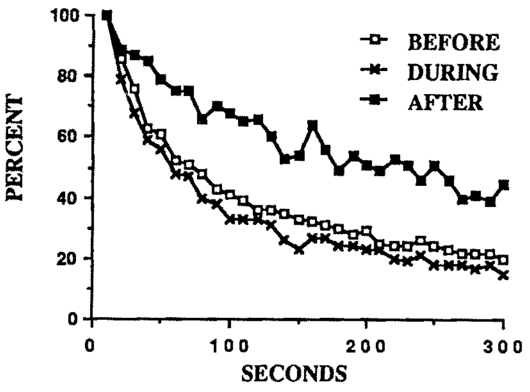

Fig 1. Example of time course of xenon clearance before, during, and after exposure to cold, dry air. Measurements of radioactivity were made at 10-second intervals and expressed as percent of initial measurement.

fined as an increase in symptoms associated with a twofold rise in the levels of histamine and N-α-tosyl-L-arginine methyl ester–esterase activity in nasal lavages recovered 10 minutes after the challenge, compared to an equivalent challenge with warm, moist air. All subjects gave informed consent before participating in the study, and the study was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins Hospital.

The experiments were conducted in the Nuclear Medicine Division of the Department of Radiology. Each subject reported to the study room and, after becoming acclimatized, lay supine on a stretcher for the duration of the experiment. The technique for measuring xenon clearance approximated that described by Bende et al.[9] In brief, a mixture of xenon in saline with a specific activity of 1.5 to 2 mCi/mL was prepared in the Nuclear Medicine Radiopharmacy Laboratory. After preparation, 0.1 mL of this mixture (100 mCi) was injected slowly into the left inferior turbinate. For these patient studies, a large field-of-view gamma camera fitted with a general all-purpose parallel hold collimater interfaced to a dedicated computer was used. Patients were injected under the gamma camera and were not moved until completion of the study. The data were acquired by use of a 1-second frame mode for 10 minutes. The amount of activity remaining was determined at 10-second intervals for the next 10 minutes. The half-life for clearance was determined from the first 5 minutes. Other measurements, such as the half-life for 10 minutes or between 1 and 5 minutes, yielded similar results and will not be reported. Measurements in which total clearance occurred in less than a minute were eliminated because similar results were shown to occur when xenon in saline was instilled, instead of injected, onto the inferior turbinate.

After a 10-minute interval, the subject inhaled CDA (−5°C to 0°C, <10% humidity) at a flow rate of 12 L/min for 15 minutes. Subjects inhaled the conditioned air through a pediatric face mask and exhaled through the mouth.

The CDA stimulus was interrupted briefly after 5 minutes, and another injection of xenon solution was made. The stimulus was reapplied immediately postinjection and continued while the measurement of clearance was made. The subjects inhaled CDA for a total of 15 minutes. Ten minutes after the stimulus was removed, while the clinical response was occurring, the third measurement of clearance was made. In total, we made measurements of xenon clearance before, during, and after exposure to CDA. Similar measurements were made at identical time points in equivalent locations within the inferior turbinate on another day, with the subjects inhaling room temperature air. Previous studies showed the responses to inhaling warm, moist air and room temperature air to be equivalent.[12]

As a pharmacologic control for the technique, we studied the effect of a vasoconstrictor and a vasodilator. Xenon clearance was measured in four subjects before and 10 minutes after topical administration of 0.1 mL of oxymetazoline 0.05%, a vasoconstrictor. In two subjects we injected histamine, a vasodilator, simultaneously with xenon solution and compared the change in clearance to a baseline measurement made 15 minutes before.

By means of an analysis of variance we evaluated the results between the two experimental conditions and between the different measurements performed on the same day. Data are presented as the mean ± SEM. Two subjects were eliminated from the final analysis because of incomplete data.

RESULTS

The topical application of oxymetazoline decreased the rate of clearance (half-life before, 59±12 seconds; after, 80±21 seconds), whereas histamine increased the rate of clearance (half-life before, 45±5 seconds; after, 35±2 seconds).

Although we did not document the clinical response to CDA by mediators, all subjects reported a clinical response to the challenge similar to the one noted during their screening challenge. The effect of inhaling CDA on xenon clearance in one individual is illustrated in Fig 1. The clearance curves obtained before and during challenge showed similar patterns. In contrast, the curve obtained 10 minutes after the stimulus, during the clinical response, showed a marked prolongation of xenon clearance; ie, in an equivalent period of time, less of the injected xenon was removed from the nose. The results for the group (Fig 2) were similar to those of the individual in Fig 1. On the day when CDA was inhaled, the half-life before injection was 56±6 seconds, and it remained essentially unchanged during inhalation of the stimulus (41±5 seconds). Ten minutes postchallenge the rate of clearance was decreased significantly ($p<.01$), to 110±31 seconds.

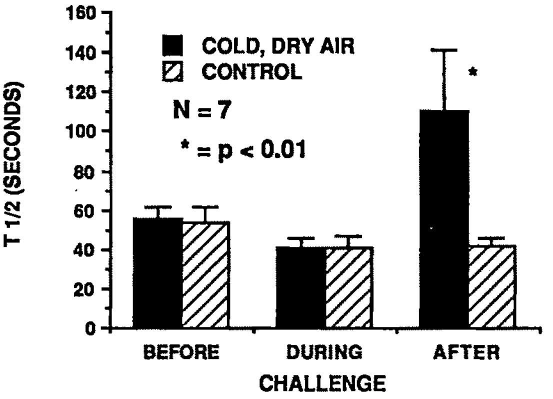

Fig 2. Xenon clearance (mean ± SD) for seven subjects expressed as half-life (T½) in seconds during first 5 minutes postinjection. Measurements were made before, during, and after exposure to cold, dry air.

On the control day, the equivalent half-life in seconds during the inhalation of room air was 54 ± 8, 41 ± 6, and 42 ± 4, respectively.

DISCUSSION

The results of this study are clear: the inhalation of CDA has no effect on xenon clearance during stimulus presentation, but significantly reduces clearance during the clinical response to the inhalation of CDA. Since investigators studying xenon clearance equate it with changes in blood flow, our results imply that nasal blood flow remains unchanged during the inhalation of CDA, but decreases significantly during the clinical response. We should interpret these results as implying that the cooling and evaporative water loss accompanying the inhalation of CDA do not alter the superficial circulation, and that as the subject clinically responds to the stimulus by releasing vasoactive inflammatory mediators, blood flow is reduced. Since blood flow is the important variable and the rate of xenon clearance from the nose has no significance per se, we must examine the assumption that xenon clearance measures nasal blood flow.

The nasal vasculature presents a unique organization of blood vessels. The arterial supply arises primarily from the external carotid artery (the sphenopalatine artery, the angular branch of the facial artery, and the descending palatine artery), with a substantial contribution from the internal carotid artery (anterior and posterior ethmoid arteries). The patency of arterial anastomoses is demonstrated by the viability of the nasal mucosa after ligation of any branch, including the sphenopalatine artery, the largest contributor. The venous drainage, like the arterial blood supply, involves multiple anastomosing vessels. Blood enters veins not only from capillary beds but also directly from arteries. Anteriorly, the nasal veins communicate with the palatine veins below, and laterally, they communicate with the angular and anterior facial veins. The majority of venous drainage occurs via the sphenopalatine and ethmoidal veins. The latter pass through the cribriform plate and drain into the sagittal sinus.[13] The relative contribution of each artery and vein and how these contributions change with physiologic events, such as a localized antigen challenge, remains to be determined.

The majority of capillaries within the nose are located superficially in the nasal mucosa and around the nasal glands. The capillaries have fenestrations that face toward the epithelial surface. Cauna[14] believes that these are the major site for transudation. The postcapillary venules can drain either into sinusoids or into the collecting veins. The sinusoids, like the erectile tissue of the penis, can hold large quantities of blood. The amount of blood within these valveless sinusoids, whose rate of drainage is regulated by cushion or throttle veins, affects airflow as reflected in the measurement of nasal airway resistance.[15] The cushion veins also are believed to play a role in the absorption of extracellular fluid. Arteriovenous anastomoses bypass both the sinusoids and the capillaries, permitting the direct admixing of arterial and venous blood. Their function is unknown.[16] The entire vasculature is richly innervated by nerves reported as predominantly sympathetic and parasympathetic in origin,[15,16] but our understanding of the role of the nonadrenergic, noncholinergic system probably will increase as modern techniques for evaluating the neuronal system are applied to the nasal mucosa. This cursory description of the anatomic complexity of the nasal vasculature suggests some of the difficulties in interpreting the results of nasal xenon clearance.

The measurement of xenon clearance postinjection has been used for years as a technique to estimate blood flow. Bende et al[9] first applied this technique to the study of nasal blood flow. In a series of experiments, they have shown that 1) in laryngectomized patients, xenon clearance occurs primarily via the lungs, suggesting that limited clearance occurs by contact with air within the nasal cavity[17]; 2) injected, not topically applied, histamine increases xenon clearance[9]; 3) α2-agonists, but not α1-agonists, decrease clearance[18]; 4) corpses have a greatly decreased rate of clearance[9]; 5) the estimated rate of nasal blood flow is 40 mL/(100 g/min); and 6) xenon clearance decreases 15 minutes post–nasal challenge with antigen, remains unchanged during exercise (despite a decrease in nasal airway resistance and an increase in pulse and blood pressure), decreases during whole body cold exposure associated with a decrease in nasal airway resistance, and is unaffected by warm air exposure.[3,19] The experiments reported in this manuscript are consistent with results reported after whole body cold exposure.

The complexity of blood flow is indicated by the differences reported for blood flow measured by the different in vivo techniques. Konno et al,[11] using hydrogen clearance, reported an increase in blood flow bilaterally after unilateral antigen provocation. These results contrast with those of Holmberg et al,[19] who reported that xenon clearance, and hence blood flow, decreased bilaterally after antigen challenge. Tanimato et al,[20] using the hydrogen ion clearance technique, found regional differences in blood flow. The area under an antigen-containing disc decreased, while that at a distance increased. The differences between these results could be explained by regional changes in blood flow. We hypothesize that blood flow in the superficial capillaries increases during antigen stimulation, while pooling and margination[21] of red blood cells in the cavernous sinusoids increases. Hydrogen ion clearance may reflect changes in the superficial capillary circulation, while xenon clearance reflects the net exiting blood flow. For example, after antigen challenge superficial blood flow may increase, while exiting blood flow decreases to a greater extent; hence, xenon clearance decreases. Support for the latter statement comes from Holmberg et al.[19] Xenon clearance decreased statistically only during the time that nasal airway resistance, and hence the volume of the capacitance vessels, was increasing. When nasal airway resistance stabilized, xenon clearance returned to basal conditions. A similar event is likely to be occurring during the nasal challenges with CDA that we report. Thus, decreased xenon clearance may reflect net changes in the exiting blood flow, rather than regional changes (which may be more important in understanding the physiology of the response).

The technique of measuring nasal blood flow by laser-Doppler velocimetry agrees with the xenon clearance method in estimating the basal blood flow to be 40 mL/(100 g/min).[10] It has not been applied, however, to the study of blood flow during nasal challenge with antigen. Nasal challenge with methacholine had no effect on the measurement of blood flow by laser-Doppler velocimetry, whereas oxymetazoline decreased flow.[10] Leukotriene D4 induced an increase in blood flow without a concomitant change in nasal airway resistance.[22] Olsson et al[23] observed that blood flow decreased when subjects had their feet immersed in cold water and suggested that the laser-Doppler evaluated superficial blood flow, while xenon clearance reflected mean blood flow. It would be interesting to know the effect of inhaling CDA on blood flow as determined by the laser-Doppler.

The complexity of nasal blood flow is illustrated further by the experiments of Änggard[24] in which he used microspheres to study blood flow in cats. Sympathetic stimuli induced a redistribution of blood flow through arteriovenous anastomoses without an effect on the capillary blood flow. It would be interesting to know the results of xenon clearance under the same experimental circumstances. Other potential confounding variables in understanding the effect of xenon clearance relate to the effects of factors carried through the bloodstream; for instance, orally ingested phenylephrine induces a decrease in nasal airway resistance. Theoretically, mediators released by mast cells in response to CDA could influence the nasal vasculature at distant sites. Furthermore, we should not underestimate the importance of the physiologic contributions to blood flow, ie, blood pressure and vascular resistance, or the direct or indirect effects of pH or hypoxia.[25]

In sum, the results of our study are clear: xenon clearance is decreased during the response to the inhalation of CDA. The physiologic interpretation of these results is less clear. We believe that the complexity of nasal blood flow needs further evaluation in vivo before changes in xenon clearance or any of the other currently available measures can be equated with changes in nasal blood flow. Further studies are needed to verify current techniques or to develop new ones before we can appreciate fully the complexity of blood flow during nasal physiologic responses.

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INTERNATIONAL CONFERENCE AND WORKSHOP HEAD AND NECK CANCER REHABILITATION

An International Conference and Workshop on Head and Neck Cancer Rehabilitation will be held March 14-18, 1990, at the Ritz Carlton Hotel in Dearborn, Michigan. For further information, contact Department of Otolaryngology, Wayne State University, School of Medicine, 4201 St Antoine, 5E–UHC, Detroit, MI 48201; (313) 577-0804.

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IMAGING CASE STUDY OF THE MONTH

RHINOCEREBRAL MUCORMYCOSIS: COMPUTED TOMOGRAPHIC IMAGING OF CAVERNOUS SINUS THROMBOSIS

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PATIENT

A 16-year-old boy was first admitted to the University of Missouri–Columbia Hospital on April 19, 1986, with a history of being well until January 1986, when he was judged to have cardiac failure and pulmonary edema. A presumptive diagnosis of an autoimmune cardiomyopathy led to therapy with Imuran and steroids along with Lasix and digitalis. On April 7, he was placed on a regimen of heparin and coumadin for a pulmonary infarct. On April 17, the antibiotic Cefulac was added to the steroid therapy. The patient fell from bed on April 18, striking his head on the pole of the intravenous apparatus. The following day he had the acute onset of proptosis, pupillary dilation, and blindness of the left eye. Extraocular muscle movements were intact, without evidence of cellulitis. At this point he was transferred to the University of Missouri–Columbia Hospital.

On admission, the patient had a pulse of 120 beats/min, systolic blood pressure of 68 mm Hg, and a temperature of 36.4°C (97.6°F). Results of a computed tomographic (CT) scan performed the same day were interpreted as negative, but it was an inadequate study because of coughing. Proptosis, periorbital edema, corneal ulceration, and Marcus Gunn's sign of the pupil were noted in the left eye. Examination of the right eye yielded normal results. Hemorrhagic gingiva and pharyngeal mucosa were present on examination, as was decreased sensation in the area served by the ophthalmic division of the left trigeminal nerve. The left corneal reflex was absent. An ophthalmologist was consulted and made the diagnosis of cavernous sinus hemorrhage and central retinal artery occlusion, most likely secondary to anticoagulation. A CT scan of the orbits without contrast on April 22 (see Figure, A) showed increased density of the left orbit consistent with trauma. The patient complained of pain in the left eye with the onset of a left facial paralysis on April 23. On the following day, left cranial nerve palsies of nerves III, IV, and VI were noted. Necrosis of the left eyelid in the medial canthal region became apparent on April 27, and sinus radiographs demonstrated opacification of the left frontal and ethmoid sinuses.

Otolaryngology consultation was requested. Nasal examination revealed purulence and blood with crusting bilaterally, but no evidence of necrosis. Results of a fungal stain were negative. Computed tomography was repeated on April 27 (see Figure, B) and showed air medial to the globe outside the muscle cone, soft tissue thickening anterior to the nasal bones, fluid level in the frontal and left ethmoid sinuses, and thrombosis of the left cavernous sinus. The patient became very lethargic. He was placed on a regimen of amphotericin B, metronidazole, and cefotaxime sodium. A left external ethmoidectomy, left orbital exenteration, and debridement of left periorbital and midfacial necrosis was performed. Mucormycosis was diagnosed on frozen section and was present on the exposed dura posteriorly. Within 3 days, on May 1, duskiness of the right periorbital region appeared, with loss of light perception in the right eye.

On May 2, a CT scan revealed irregularly decreased densities in the left basal ganglia with compression of the left lateral ventricle (see Figure, C). On May 3, a right hemiparesis was apparent with a frozen globe and minimal pupillary reaction in the right eye. The patient died on May 8.

Postmortem examination revealed involvement of the left optic nerve and optic chiasm, left cerebral peduncle, and left basis pontis with mucormycosis. Cerebritis involved the basal ganglia, left thalamus, and left hippocampus. Left uncal herniation and pulmonary mucormycosis were also present.

DISCUSSION

This case demonstrates an unusual case of mucormycosis. The findings in the first two CT scans were

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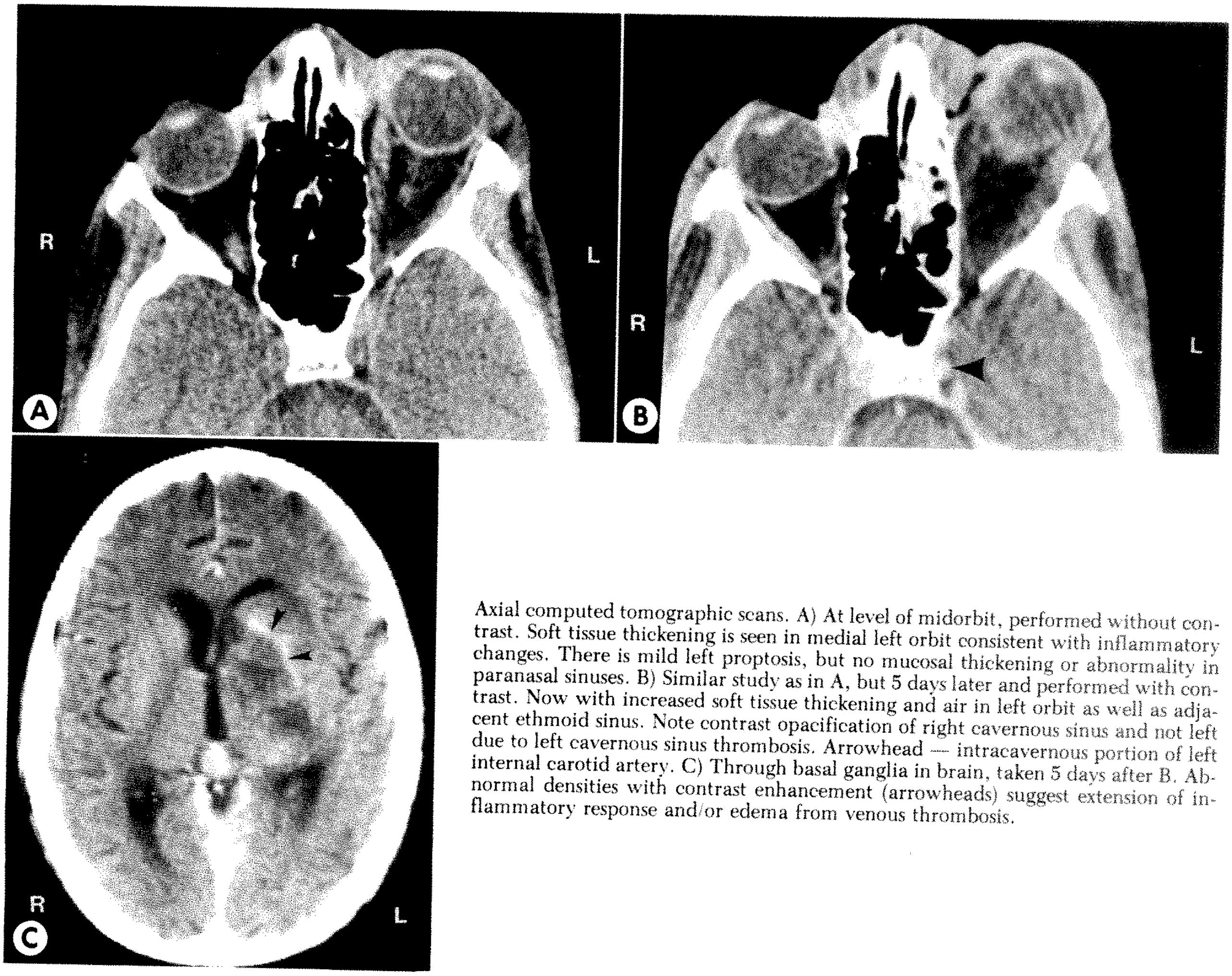

Axial computed tomographic scans. A) At level of midorbit, performed without contrast. Soft tissue thickening is seen in medial left orbit consistent with inflammatory changes. There is mild left proptosis, but no mucosal thickening or abnormality in paranasal sinuses. B) Similar study as in A, but 5 days later and performed with contrast. Now with increased soft tissue thickening and air in left orbit as well as adjacent ethmoid sinus. Note contrast opacification of right cavernous sinus and not left due to left cavernous sinus thrombosis. Arrowhead — intracavernous portion of left internal carotid artery. C) Through basal ganglia in brain, taken 5 days after B. Abnormal densities with contrast enhancement (arrowheads) suggest extension of inflammatory response and/or edema from venous thrombosis.

nonspecific enough that the appropriate diagnosis was not made. One must maintain a high index of suspicion for mucormycosis based on a clinical differential diagnosis. Computed tomographs of sinuses involved with mucormycosis characteristically demonstrate thickening of the sinus mucosa and bone destruction without air-fluid levels.[1,2] The absence of sinus involvement on these initial scans is unusual, and if it had been present, sinus involvement likely would have led to an earlier diagnosis of mucormycosis. The CT scans demonstrate progression of the disease, with the final CT demonstrating cavernous sinus thrombosis along with the cerebral mass effect.

Multiple radiographic imaging methods have been employed to demonstrate cavernous sinus thrombosis, including angiography, digital orbital venography, CT, and magnetic resonance imaging.[3-6] This represents the first known CT documentation of cavernous sinus thrombosis in the otolaryngology literature.

The typical CT findings to be demonstrated in cavernous sinus thrombosis include multiple irregular filling defects (low attenuation) to complete nonopacification of one or both sides of the cavernous sinus when contrast is employed. There may be associated thrombosis of the intracavernous portion of the internal carotid artery, cerebral infarct, prominent superior ophthalmic vein, exophthalmos, and periorbital swelling.

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PATHOLOGY CONSULTATION

LYMPHOEPITHELIAL CYSTS OF THE PAROTID REGION: A "NEW FACE" ON AN OLD LESION

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Lymphoepithelial cysts of the parotid gland and its lymph nodes have been known for nearly 100 years, but only in the past half-decade have they gained clinical prominence, if not significance. The lymphoepithelial cysts can now be added to the growing list of clinicopathologic manifestations of human immunodeficiency virus–associated diseases.

The benign and cystic salivary gland lesions known as lymphoepithelial cysts have two almost exclusive sites of origin: the oral cavity and the parotid gland and its environs.[1] In each site, two histologic components constitute the lesions: an intrinsic lymphoid tissue and epithelial cysts whose linings range from modified ductal to squamous cells.

In the oral cavity, where their origin is considered to be from dilated crypt epithelium in areas having an intimate epithelial-lymphoid tissue association, the lymphoepithelial cysts have a predilection for the floor of the mouth (50% to 80%).[2] They also can occur in the ventral tongue, soft palate, and occasionally in the palatoglossal fold, buccal mucosa, and lips. Men are affected more than women (8:1), and the cysts are diagnosed most often in patients between the ages of 20 and 60 years (mean, 30 years).

Lymphoepithelial cysts of the parotid gland region take origin from enclaved salivary ducts within parotid or paraparotid lymph nodes or in relation to noninflammatory-based lymphoid tissue within the gland.[1] Their histogenesis is likened to that accepted for Warthin's tumors.

As judged by the literature prior to the last 5 years, lymphoepithelial cysts of the parotid gland and environs are uncommon (see Table[3-6]), an estimate that may be misleading because of their usually asymptomatic qualities.

The number of reported cases in the past 5 years, however, has already exceeded earlier estimates of their frequency. This clinical, radiographic, and pathologic prominence relates solely to a putative relationship with human immunodeficiency virus (HIV) infection.[7-9] The cysts have occurred in HIV antibody–positive patients, in subjects at risk for the acquired immunodeficiency syndrome (AIDS), and in patients with AIDS. In the event, lymphoepithelial cysts can now be added to the several lesions producing parotid gland swellings in patients with AIDS or AIDS-related complex (ARC). These include parotid gland lymphadenopathy (follicular hyperplasia, lymphomas, or, rarely, intranodal Kaposi's sarcoma), chronic parotitis, and a lymphoepithelial sialadenopathy without the nonsalivary components of Sjögren's syndrome.[10,11]

Clinical and demographic differences between pre-HIV and HIV-associated lymphoepithelial cysts of the parotid region are those related to the population at risk for AIDS and ARC. The HIV-associated lymphoepithelial cysts have occurred to date only in men. In the pre-HIV era, the lesions manifested a 3:1 male preponderance. The HIV-associated lymphoepithelial cysts are more often bilateral, and in keeping with the patients' risk factors are also often found with a synchronous cervical adenopathy and/or other lymphadenopathy. A significant number of patients have been prisoners and intravenous drug abusers. The age of patients at the time of clinical detection of the cysts has not varied: 20 to 40 years.

Except for a perceived greater proliferative appearance in HIV-associated epithelial cysts, the epithelial linings of the cysts in the two groups do not differ in the degree of squamous metaplasia or thickness (see Figure; A,B). We have a subjective impression that focal mucosal ulcers and pericystic granulomatous reactions are more often seen with HIV-associated cysts (see Figure, C).

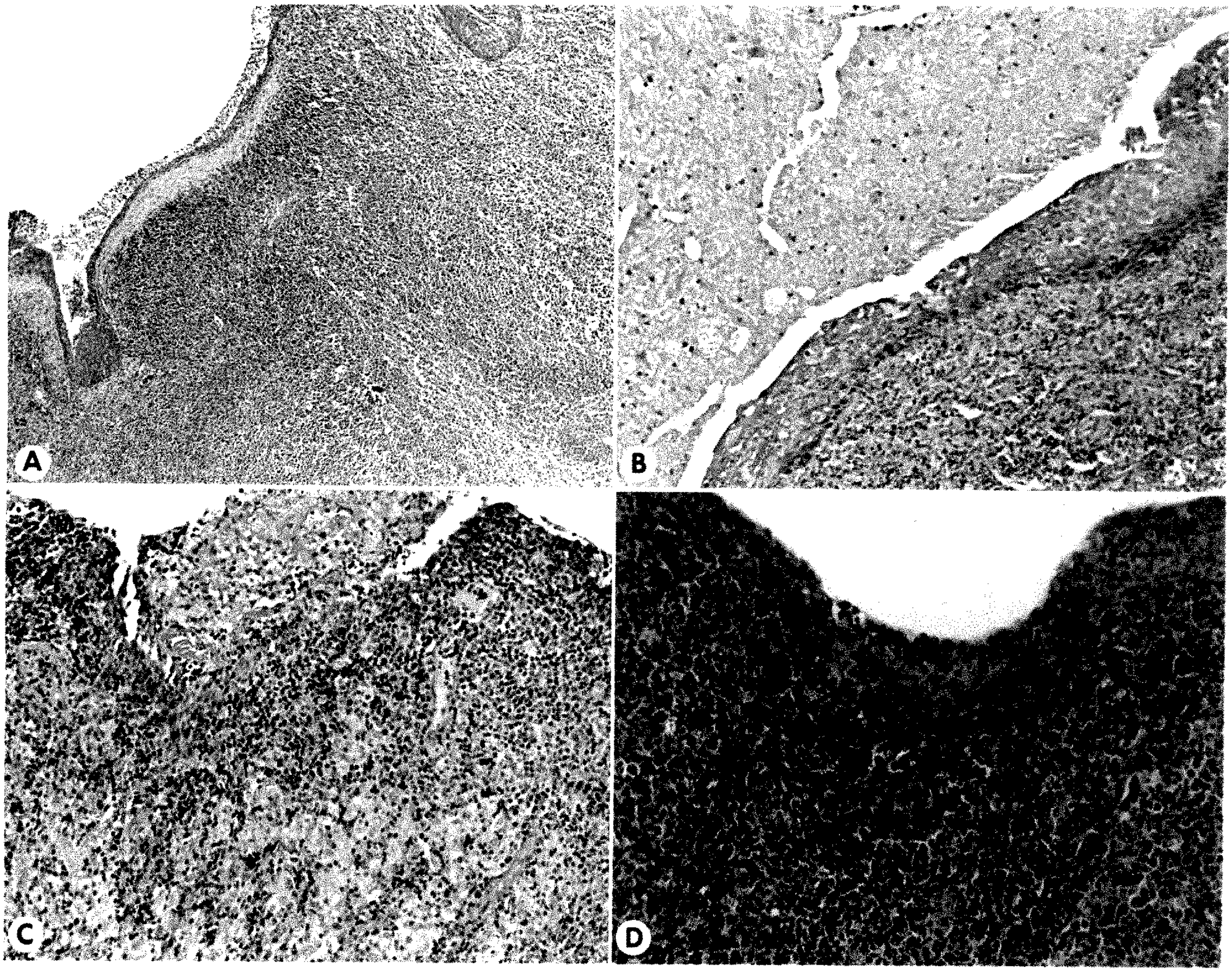
It is the lymphoid component of the HIV-asso-

LYMPHOEPITHELIAL CYSTS OF THE PAROTID GLAND IN THE PRE-HUMAN IMMUNODEFICIENCY ERA

Author	*No. of Parotidectomies*	*Lymphoepithelial Cysts*	
		No.	*%*
Lathrop[3]	243	3	1.2
Eneroth[4]	864	5	0.6
Richardson et al[5]	708	16	2.3
Cohen et al[6]	137	1	0.7

From the University of Texas M. D. Anderson Cancer Center, Houston.

REPRINTS — John G. Batsakis, MD, Division of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston TX 77030.



Lymphoepithelial cysts of parotid gland lymph node. A) From human immunodeficiency virus–positive drug abuser (H & E, original x60). B) From patient with acquired immunodeficiency syndrome (H & E, original x140). Lymphoid cell hyperplasia lies beneath metaplastic (squamous) lining of cyst. Grumous duct contents are in lumen of cyst. C) With mucosal ulcer in lining (H & E, original x160). Note epithelioid cell reaction in underlying lymphoid tissue. D) Manifesting focal proliferation of epithelial lining and subjacent follicular hyperplasia of lymphoid tissue (H & E, original x160).

ciated lymphoepithelial cysts that manifests the greatest divergence from pre-HIV lymphoepithelial cysts. The findings cover the gamut of those seen in the immunodeficiency syndrome: from lymphoid hyperplasia, often of a florid follicular type, to lymphoid depletion and lymphoma (see Figure, D).

Lymphoepithelial cysts of the parotid gland and its lymph nodes are to be distinguished from the lymphoepithelial lesion and from a Warthin's tumor with squamous metaplasia. A papillary configuration and oncocytic residues are not found in lymphoepithelial cysts. Epimyoepithelial islands (see Figure, D) can be found in the lymphoid tissue of a lymphoepithelial cyst, but the multiple cysts, the principally intranodal location of the cysts, and definite squamous metaplasia remove the lesions from a lymphoepithelial lesion classification.[1,12,13]

Lymphoepithelial cysts of the parotid gland and its environs are not newly identified lesions; Hildebrant[14] reported the first example in 1895. They have, however, acquired a "new face" and prominence because of their relationship with HIV infection. Whether this clinical prominence is due only to the hyperplasia of the lymphoid tissue of the cysts or to a combined epithelial and lymphoid proliferation has yet to be determined.

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The Third International Symposium and Workshops on Surgery of the Inner Ear will be held July 29-August 4, 1990, in Snowmass-Aspen, Colorado. For further information, contact Maurine Taylor, c/o I. Kaufman Arenberg, MD, 300 East Hampden Avenue, Suite 401, Englewood, CO 80110.

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The University of Iowa Department of Otolaryngology–Head and Neck Surgery and the International Cochlear Implant Association will hold the Second International Cochlear Implant Symposium in Iowa City on June 4-9, 1990. The symposium will focus on basic science aspects of electrical stimulation on the auditory system, new cochlear implant strategies, clinical application in both adults and children, and rehabilitation and educational issues. Please submit abstracts to Bruce J. Gantz, MD, Department of Otolaryngology–Head and Neck Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

BOOK REVIEWS

Middle Ear Implant: Implantable Hearing Aids

J.-I. Suzuki, ed. Vol 4 in *Advances in Audiology*. M. Hoke, series ed. Hard cover, illustrated, indexed, 166 pages, 1988. Karger, New York, NY, $98.

While reading this book, I could not help being tempted to have a choir of hearing-impaired spirits awaken Alexander Graham Bell with a chorus of "If You Could See Us Now!". The progress in the habilitation of hearing-impaired people since Bell's innovative work, specifically the rapidity with which improvements in amplification devices have been made, is staggering. Dr Suzuki addresses the latest developments in amplification devices in this book.

Other than the obvious cosmetic advantages of implantable hearing aids, their primary benefit is in the transmission of high-fidelity, low-distortion sound directly to the inner ear. The handicaps of realizing their maximum benefits include the lack of a reliable and durable ossicular vibrator, the unavailability of external adjustments to accommodate any change in the patient's hearing, and the requirement for additional surgery in 2 to 3 years for replacement of the internal battery. These issues are discussed in the text, which also includes the results of a 5-year study in Japan of the totally implantable and partially implantable middle ear devices, studies with an electromagnetic induction hearing system, the development of a semi-implantable hearing device in the United States, and a percutaneous transducer developed in Sweden.

Before the maximum potential in implantable hearing devices is achieved, several goals must be met: 1) a long-acting power source, 2) an implantable magnet, 3) a mechanical device to drive the stapes, 4) improvement in the microphone, and 5) accommodations for small ear canals and those with deviations.

This text covers the field of implantable hearing devices completely in just 166 well-planned and well-written pages that will engage the reader's interest.

DENNIS G. PAPPAS, MD
Birmingham, Alabama

Tumors of the Larynx and Hypopharynx

O. Kleinsasser. Hard cover, illustrated, indexed, 349 pages, 1988. Thieme Medical Publishers, New York, NY, $145.

Oskar Kleinsasser sets out to provide a text covering the various aspects of the larynx and hypopharynx. He has succeeded admirably. This rather complete work is quite readable, partially owing to the able translation from German into English by Philip Stell.

The text goes into particular detail about the epidemiology, etiology, and pathogenesis of tumors in the larynx and hypopharynx. In an especially strong part of the book not only are the well-known carcinogenic agents tobacco and ethanol discussed, but also the chemical, occupational, environmental, and social factors inducing tumor formation. The pathology and biology of these neoplasms are described, including the immune reactions associated with cancer formation. The section called Special Morphology is striking because of the superb illustrations that amplify the text.

The diagnostic and therapeutic modalities are sufficiently discussed. Perhaps a more detailed description along with illustrations of computed tomographic scanning and magnetic resonance imaging for the evaluation of primary neoplasms of the larynx and hypopharynx would have been beneficial. The use of scanning has certainly altered the diagnostic capabilities in this area more than any other single factor to date. These details, however, can be further elucidated in a head and neck radiology text or by use of the extensive reference list.

Special attention is devoted to the section on voice preservation procedures, including partial laryngectomy (hemilaryngectomy, frontolateral and anterior, supraglottic, and three-quarter) as related to both laryngeal and pyriform fossa carcinomas. A wide array of instructive diagrams and illustrations accompanies the narrative. Different methods of neck dissection are described, including the doubtful utility of the supraomohyoid neck dissection for tumors in this region of the aerodigestive tract. The use of radiation therapy and chemotherapy is concisely discussed, along with the controversies surrounding the preference of one modality over another and the timing of these agents with respect to the surgical excision.

Rehabilitative techniques and follow-up care are covered to the point of discussing the implications of postlaryngectomy depression on vocal rehabilitation. Reconstructive techniques following total pharyngectomy, notably gastric pull-up, microvascular jejunal free flap interposition, and myocutaneous flaps, are adequately covered.

A comprehensive section of less commonly encountered tumors, including minor salivary, neural, lymphoreticular, fibrous, vascular, and other mesothelial entities, along with neoplasms that are metastatic to the larynx itself, is certainly a welcome addition to the clinician's fund of knowledge.

The reference sections following each area of discussion are uniformly superb and provide an up-to-date, global compendium for future reading. The text should be a valuable addition to the otolaryngologist's library.

DAVID KAUFMAN, MD
New York, New York

The CO2 Laser in Otolaryngology and Head and Neck Surgery

V. H. Oswal, H. K. Kashima, and L. M. Flood, eds. Hard cover, illustrated, indexed, 200 pages, 1988. John Wright, Cambridge, England, $95.

This multi-authored text provides a broad review of the principles of laser surgery in otolaryngology today, as well as the specific procedures and techniques for which it is used.

The chapters were written independently of each other and are for the most part concise and easily readable. As inevitably occurs in a text such as this, some overlap of information occurs among chapters throughout the book. In some cases this serves the useful function of emphasizing universally accepted principles, such as the need to protect endotracheal tubes near a laser operative field. In other cases conflicting opinions are expressed, and the reader is left to draw his or her own conclusions. For example, in the event of an endotracheal tube ignition, one author advocates the immediate removal of the tube as the first step in management, while another states that first the fire should be extinguished in order to ensure continued control of the airway. This reviewer found the arguments for the former approach more compelling.

The chapter on laser safety in the operating room includes an excellent review of the relative risks and dangers of the carbon dioxide and neodymium:yttrium aluminum garnet lasers to patients and operating personnel. It also provides extensive and comprehensive guidelines for reducing the dangers inherent in laser use as well as for establishing hospital policies in this regard.

Some of the technical information presented occasionally becomes a bit abstruse; and several chapters would have benefited from a greater use of illustrative diagrams, especially those chapters dealing with the broad variety of specific laser surgery techniques that this book covers. Also, the role of the CO2 laser in the treatment of carcinoma of the upper aerodigestive tract, while still controversial for many head and neck surgeons, is here taken for granted as accepted.

This volume offers a worthwhile and up-to-date overview of a mature surgical technology that has lived up to all of its early promises.

KENNETH L. SCHNEIDER, MD
New York, New York

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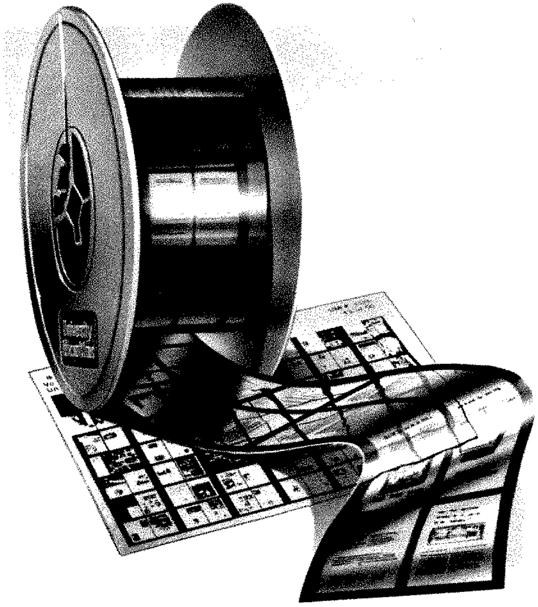

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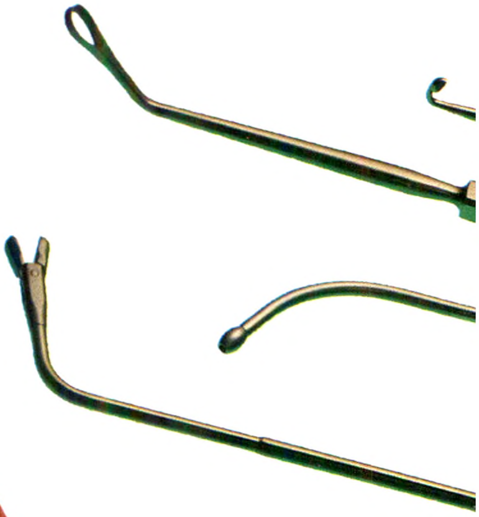

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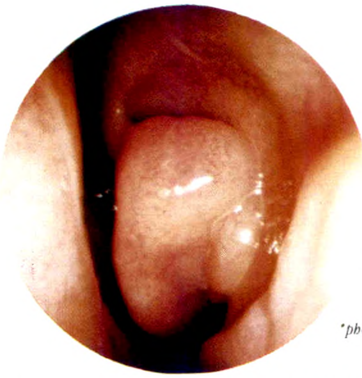

*Concha bullosa on left side bulging into lateral nasal wall. Entrance to middle meatus blocked and a polyp is arising from the contact area.**

**photo by Professor H. Stammberger*

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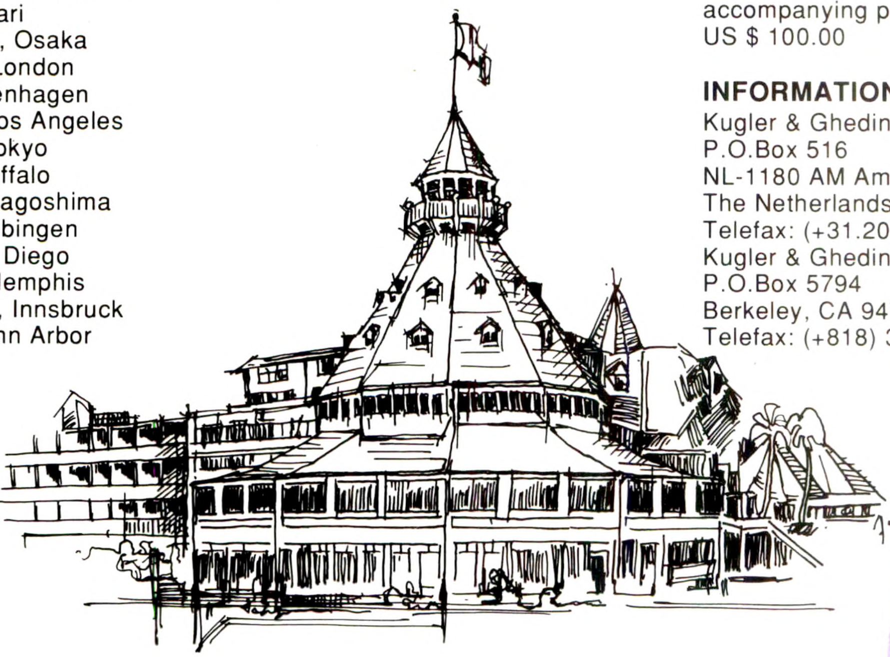

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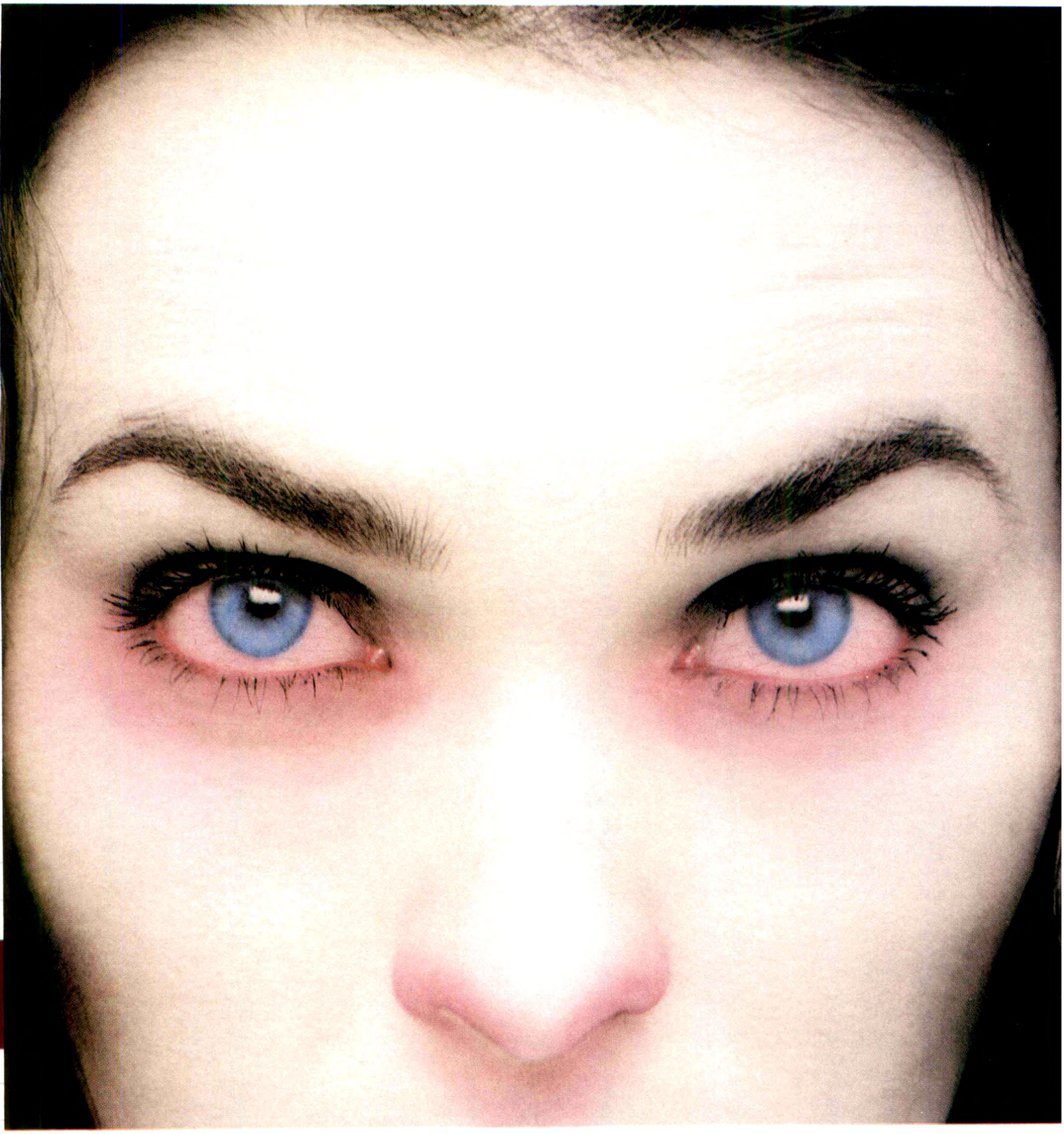

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REINNERVATION OF THE CANINE POSTERIOR CRICOARYTENOID MUSCLE WITH SYMPATHETIC PREGANGLIONIC NEURONS

IAN N. JACOBS, MD
BEI-LIAN WU, MD
IRA SANDERS, MD
HUGH F. BILLER, MD
NEW YORK, NEW YORK

This experiment investigated the reinnervation of the canine posterior cricoarytenoid (PCA) muscle with preganglionic neurons of the sympathetic nervous system. Six dogs had their right recurrent laryngeal nerve (RLN) sectioned. Four of these dogs had the sympathetic cervical trunk (SCT) implanted into the right PCA muscle, and the two remaining dogs served as denervated controls. Four months later all dogs underwent videolaryngoscopy, electromyography, and electrical stimulation of the SCT. The PCA muscles were excised, sectioned, and stained for glycogen and ATPase. All four experimental PCA muscles demonstrated electrically evoked abduction and tonic electromyographic activity. In two of the specimens, staining (ATPase and PAS) revealed areas of reinnervation with fiber type grouping and glycogen depletion. These results are consistent with the successful reinnervation of the PCA muscle. Further refinement of this technique could be of benefit to patients with bilateral vocal cord paralysis.

KEY WORDS — posterior cricoarytenoid muscle, recurrent laryngeal nerve, reinnervation, sympathetic cervical trunk.

INTRODUCTION

Bilateral vocal cord paralysis (BVCP) leads to significant airway compromise. Tracheotomy often is required, but is an unsatisfactory long-term solution. Lateralization procedures such as arytenoidectomy[1] or arytenoidopexy[2,3] can alleviate the airway symptoms, but may leave patients with a weak and breathy voice and predispose them to aspiration.

The cause of BVCP is a functional destruction of both recurrent laryngeal nerves (RLNs) such as after thyroidectomy. Reanastomosis of the severed ends of the RLN[4-7] or transposition of extrinsic nerves to the main RLN trunk[8-11] leads to misdirected reinnervation of abductors and adductors. This results in synkinesis of the laryngeal muscles and a functionally useless larynx.

Recent experimental research has focused on the selective reinnervation of the posterior cricoarytenoid (PCA) muscle, which is the main abductor of the larynx. There are two basic ways of reinnervating this muscle. One method is either the anastomosis of the reinnervating nerve to the cut RLN with the adductor branches ligated or the direct anastomosis of the nerve to the abductor branch of the cut RLN. The second method is the direct implantation of either the reinnervating nerve or a neuromuscular pedicle (NMP) into the PCA muscle.

The selection of a nerve for PCA muscle reinnervation is based on several criteria. First, the nerve should have inspiratory activity, with minimal activity at other times such as during phonation. Second, the nerve should be in close proximity to the PCA muscle and have a sufficient number of neurons to reinnervate it. Third, the sacrifice of the nerve should not cause a deficit worse than the symptoms of BVCP.

The best inspiratory signal is present in the phrenic nerve.[12-15] In 1970, Fex[16] demonstrated vocal cord abduction after direct implantation of the phrenic nerve into the PCA muscle. Crumley et al[17] produced vocal cord abduction in dogs with a split phrenic nerve anastomosed to the RLN via a free nerve graft. Rice[18] observed good vocal cord abduction in dogs with the phrenic nerve anastomosed directly to the cut RLN. Although the loss of unilateral diaphragmatic function usually is tolerated well in healthy humans,[19] there is always the potential for a catastrophic complication. Therefore, clinicians have been very hesitant to sacrifice the phrenic nerve.

The ansa hypoglossi is another potential nerve for reinnervation. Inspiratory activity has been demonstrated in this nerve and in its branches to the sternothyroid and omohyoid muscles.[20,21] Furthermore, the sacrifice of this nerve leaves very little deficit. Hengerer and Tucker[22] demonstrated successful abduction in five dogs reinnervated with a sternohyoid NMP. Tucker[23] subsequently applied this technique to humans and claimed an 89% success rate with the omohyoid NMP. Applebaum et al[24] and May et al[25] also reported success in human studies. However, Crumley,[26] Neal et al,[27] and Rice et al[28] were never able to produce vocal cord abduction in dogs reinnervated with the NMP. Furthermore, Biller and Lawson[29] were unable to reinnervate human larynges with the NMP. Most clinicians have

---

From the Department of Otolaryngology, The Mount Sinai Medical Center, New York, New York. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The Mount Sinai Medical Center, New York, New York.

Presented at the meeting of the American Laryngological Association, San Francisco, California, April 1-2, 1989.

REPRINTS — Ian N. Jacobs, MD, 1249 Park Ave, No. 15A, New York, NY 10029.

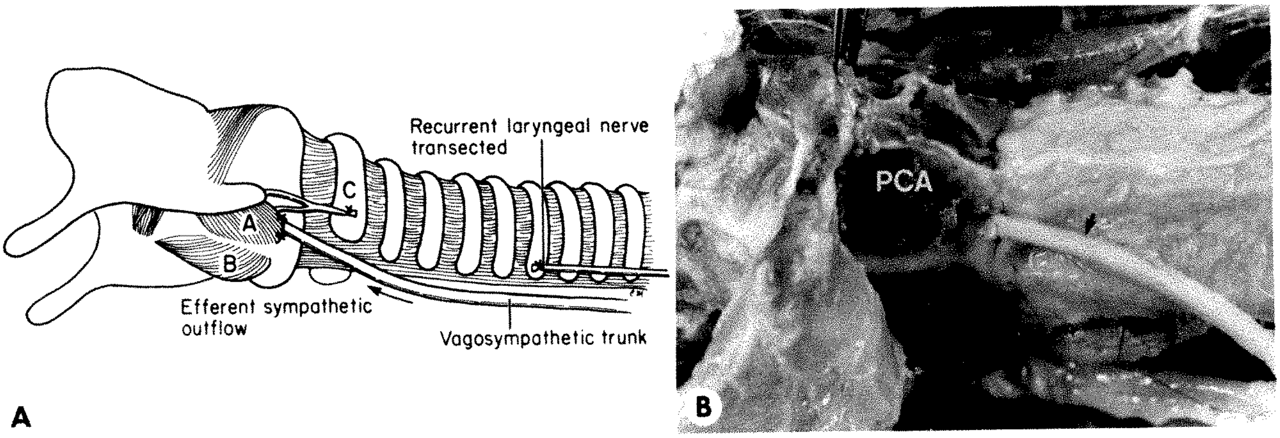

Recurrent laryngeal nerve transected
C
A
B
Efferent sympathetic outflow
Vagosympathetic trunk
A
PCA
B

Fig 1. Implantation of sympathetic cervical trunk (SCT) under right posterior cricoarytenoid (PCA) muscle. A) Artist's rendering. A — right PCA, B — left PCA, C — transected recurrent laryngeal nerve. B) Intraoperative photograph. Arrow — SCT.

abandoned the use of the NMP because of the controversy regarding its efficacy.

In this study, a new category of peripheral nerves, the sympathetic autonomics, was chosen for evaluation as a possible treatment for BVCP. Although the fact is not commonly appreciated by clinicians, the preganglionic neurons of this system are fully capable of innervating skeletal muscle.[30,31] Within the autonomic nervous system, the sympathetic cervical trunk (SCT) has several advantages. First, in the swine,[32] cat,[33-35] and human[36] the sympathetic system demonstrates inspiratory activity. Second, the SCT is easily accessible in the carotid sheath and is in close proximity to the larynx. Third, the sacrifice of the SCT causes a Horner's syndrome that is a relatively minor deficit compared to BVCP. In addition, this minor deficit might be avoided by selective use of sympathetic neurons.

This experiment was undertaken to demonstrate that reinnervation of the PCA muscle with the SCT is possible and could result in spontaneous vocal cord motion. The canine PCA muscle was selected because this laboratory has extensive experience with this model. Four dogs underwent PCA reinnervation with a direct SCT implantation. Reinnervation was documented by direct laryngoscopy, electromyography (EMG), electrical stimulation, and histologic analysis.

MATERIALS AND METHODS

Six adult male mongrel dogs underwent neck exploration under 0.5 mg/kg intravenous sodium pentobarbital anesthesia. First a low tracheotomy was performed. Then the right RLN was identified in the tracheal-esophageal groove. It was divided 3 to 4 cm below the cricoid region, and a 2-cm segment was removed. The proximal and distal cut ends were ligated and secured to the tracheal rings with a 4-0 silk suture. Four dogs underwent implantation with the SCT, while two served as denervated controls.

In the dog the vagus nerve and the SCT are combined in one structure, referred to as the vagosympathetic trunk.[37] Cervical sympathetic neurons travel in a cranial direction, while vagal efferent neurons travel in a caudal direction. In four dogs the right vagosympathetic trunk was isolated and dissected free from the carotid sheath. Positive identification of sympathetic activity was established by stimulating the vagosympathetic trunk with 5 to 10 mA while noting pupil dilatation. The trunk then was divided at the cricoid level several centimeters below the superior cervical ganglion. To prepare the PCA muscle for implantation, the inferior edge of the posterior cricoid cartilage was exposed. By use of blunt instruments the PCA muscle was undermined 2 to 3 mm off the inferior cricoid cartilage. The caudal cut end of the SCT was placed between the cartilage and the PCA muscle. Several 6-0 Prolene sutures were used to secure the nerve to the undersurface of the PCA muscle and the perichondrium of the cricoid cartilage (Fig 1A). The remaining two dogs served as denervated controls.

The overlying muscle and subcutaneous tissue was closed with interrupted chromic sutures. The skin was closed with interrupted 2-0 silk sutures. Next, the dog was decannulated and the tracheotomy site was closed with interrupted chromic sutures. Postoperatively, the dog was given 300,000 units of procaine G penicillin.

Four months later all six dogs underwent direct laryngoscopy, EMG, and reexploration of the right neck region under barbiturate anesthesia. A vaginal speculum was inserted into the mouth and opened to expose the larynx and glottis. A video camera was used to record the action of the larynx during quiet ventilation and hyperpnea caused by tracheotomy tube occlusion.

Electromyography was performed with a molded laryngeal electrode platform that fits between the postcricoid region and the esophagus to record the surface EMG of the PCA muscle.[38] Recordings were made from both the normal and the experimental sides during quiet respiration and hyperpnea. In addition, as a control at the end of the experiment, the left PCA EMG activity was abolished by injecting 5 mL of 2% lidocaine hydrochloride into the left tracheal-esophageal groove. This isolated the EMG activity of the right PCA muscle.

In the experimental dogs the SCT was identified carefully where it entered the PCA muscle (Fig 1B). The SCT trunk then was skeletonized for 4 to 5 cm caudal to the PCA muscle. The nerve was shielded electrically with a rubber sheet and stimulated with bipolar electrodes set at 10 mA and 30 Hz. Vocal cord abduction was recorded by video. The total vocal cord excursion was measured with a ruler with 1-mm gradations held directly next to the free edge of the vocal cord. In the denervated controls as well as the two normal controls, the PCA muscle was stimulated directly with the bipolar electrodes set at the same specifications. Vocal cord abduction was measured and recorded by video.

To deplete glycogen in reinnervated muscle fibers the SCT was stimulated at 15 mA and 10 Hz for 30 minutes. Then the nerve was cut and a brief EMG recording was made. The larynx was excised rapidly and stored in liquid nitrogen at −70°C. At a later time, the PCA muscles were dissected carefully from the cricoid cartilage and cut into 10-μm thick transverse sections on a microtome. The sections were placed on slides and stained for actomyosin ATPase with preincubation at pH 4.2 and 11.12. This differentiated type 1 (slow-twitch) and type 2 (fast-twitch) fibers.[39] The slides also were stained for glycogen with a PAS reagent histochemical stain.[40] The completed slides were photographed at 31.25x magnification. A clear rectangular grid with 120 2-cm^2 boxes was placed over the composite photographs of the entire PCA muscle cross section. At pH 4.2 type 1 (dark) and type 2 (light) fibers were counted in each box on the entire grid. Only discernible muscle fibers were counted. Fibers that were excessively shrunken or atrophied were not counted. The SAS/GRAPH software system, developed by the SAS Institute for data management and presentation, was used to reveal the fiber type distribution in graphical form. This system analyzes and converts bivariate data into contour plots. A previous regional histochemical study of the normal canine PCA muscle was used as a comparison.[41]

TABLE 1. AMOUNT OF VOCAL CORD ABDUCTION SEEN ON ENDOSCOPY

Dog	*Quiet Respiration (mm)*	*Hyperpnea (mm)*	*Stimulation (mm)*
Normal	0.0-2.0	2.0-4.0	2.5-4.0
SCT 1	0.0	0.75	1.0
SCT 2	0.0	0.75	0.5
SCT 3	0.0	0.5	0.5
SCT 4	0.0	0.5	0.5
DC 1	0.0	0.0	0.0
DC 2	0.0	0.0	0.0

All reinnervated dogs also had tonic oscillatory motion.

SCT — sympathetic cervical trunk, DC — denervated control.

RESULTS

Direct Laryngoscopy. In the reinnervated larynges, no vocal cord abduction was seen during quiet respiration. During hyperpnea an abduction of approximately 0.50 to 0.75 mm was observed (Table 1). In addition, each of the four dogs had a continuous oscillatory motion of the right vocal cord. There was about a 0.25-mm motion of the right vocal cord at a frequency of about 2 to 3 Hz. These parameters did not vary with the respiratory cycle. The two denervated controls did not have vocal cord motion during either quiet respiration or hyperpnea. The normal vocal cord abducted 0 to 2.0 mm during quiet respiration and 2.0 to 4.0 mm during hyperpnea.

Electromyography. The four SCT-reinnervated dogs had fine tonic activity throughout the respiratory cycle. This activity was not in phase with the electrocardiographic or the EMG activity of the contralateral PCA muscle. Two of these dogs had a phasic burst of activity during late inspiration and early expiration (Fig 2A). The left PCA muscle demonstrated normal phasic inspiratory activity. Injection of lidocaine hydrochloride into the left RLN abolished this phasic activity, but did not

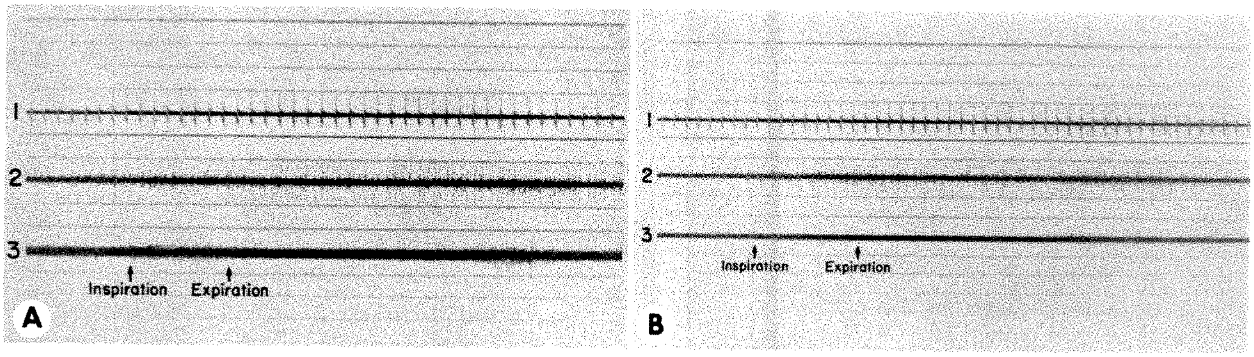


Fig 2. Electromyogram of reinnervated right posterior cricoarytenoid (PCA) muscle (2), electromyogram of normal left PCA (3), and electrocardiogram (1). A) Note increased activity during late inspiration and early expiration. B) After injection of lidocaine hydrochloride into left recurrent laryngeal nerve. Note activity remaining in reinnervated PCA.

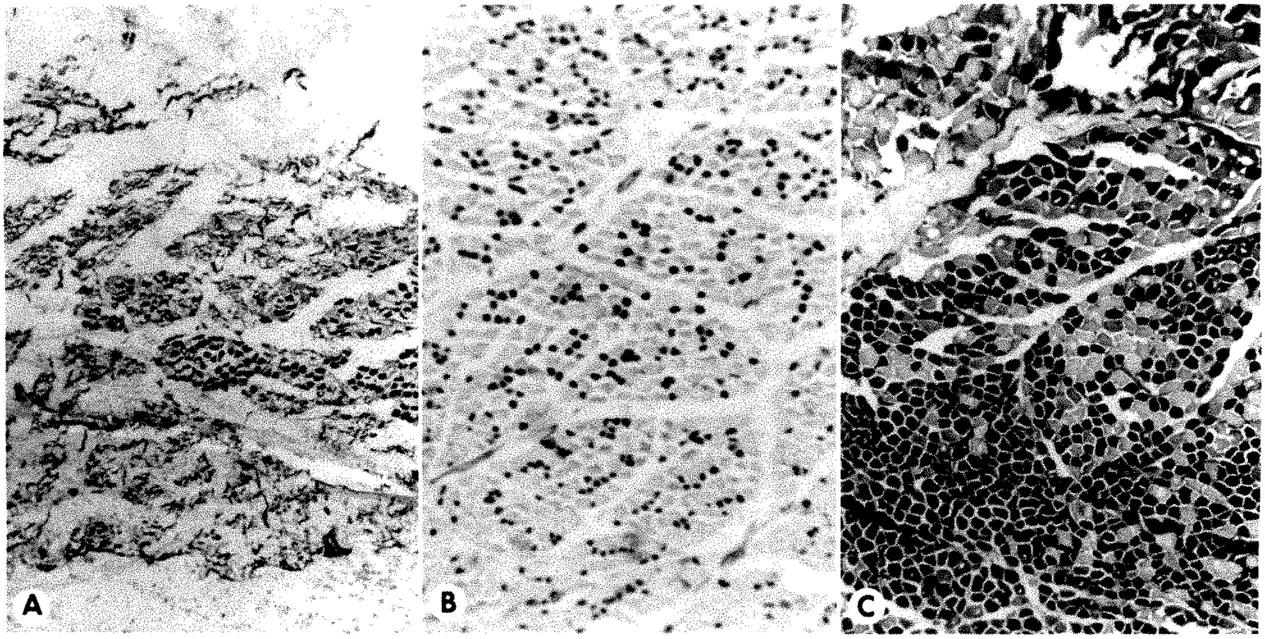


Fig 3. Posterior cricoarytenoid muscle samples stained for ATPase at pH 4.2 (original x30). A) Lateral region of denervated muscle. Note severe fiber atrophy and fibrosis. Also note preservation of small number of countable fibers in center. B) Normal muscle. Note predominance of type 2 (light) fibers in random mosaic pattern. C) Lateral region of reinnervated muscle. Note "fiber type grouping" with type 1 (dark) fiber predominance and smaller groups of type 2 (light) fibers.

change the tonic activity of the right PCA muscle (Fig 2B). Cutting the SCT abolished the activity of the right PCA muscle. Low-intensity inspiratory activity was recorded in the right PCA muscle of the two denervated controls. All activity was abolished by the injection of lidocaine into the left tracheal-esophageal groove.

Operative Findings. In all four experimental dogs the intact SCT was traced to the PCA muscle. The muscle was grossly normal in one dog and moderately atrophied in the other three. In the denervated controls, the PCA muscle was extremely atrophied and nearly transparent (Fig 3A).

In all six dogs the proximal end of the cut right RLN was found on or near the trachea. In no case was there evidence of regeneration of the RLN to the PCA muscle. Stimulation with 10 to 15 mA did not produce any vocal cord motion.

Nerve Stimulation. Stimulation of the SCT caused abductive motion in all four dogs. This ranged from 0.5 to 1.0 mm in distance (Table 1). In each case, cutting the nerve also abolished the response, and stimulation on the cut end caused an even greater abductive motion. In the denervated controls stimulation with 10 mA and 30 Hz directly on or near the muscle produced fine fasciculations but no gross motion of the muscle. The arytenoid and the vocal cord did not move at all. Stimulation of the left PCA muscle caused 2.0 to 4.0 mm of abduction.

Histochemical Findings. The ATPase-stained muscle of all four reinnervated specimens is remarkably different in appearance from that of the denervated controls. There was an average of 3,224 fibers in each reinnervated specimen, compared to an average of 7,640 fibers in the normal canine PCA muscle.[41] In contrast, there was an average of only 811 countable fibers in the denervated muscles (Table 2), and these muscle fibers were significantly smaller than those of the reinnervated specimens (Fig 3A). In addition, the percentage of type 2 (fast-twitch) fibers was notably different. A normal PCA muscle is composed of approximately 65% type 2 fibers, making it a very fast muscle (Fig 3B).[41] In contrast, the reinnervated and denervated specimens were composed of only 22.2% and 27.1% type 2 fibers, respectively.

Contour analysis revealed major changes in the arrangement of the muscle fibers after reinnervation. A normal PCA muscle has a predominance of type 2 fibers in the lateral region (Fig 4A), while the reinnervated specimens did not (Fig 4B). In addition, normal muscle fibers are interspersed in a ran-

TABLE 2. ELECTROMYOGRAPHIC AND HISTOLOGIC FINDINGS

Dog	*Electromyographic Activity*	*No. of Fibers*	*Fiber Type Grouping*	*Glycogen Depletion*
Normal	+	7,640	–	+
SCT 1	+*	2,949	+	+
SCT 2	+	7,342	+	+
SCT 3	+*	1,849	–	–
SCT 4	+	757	–	–
DC 1	–	588	–	–
DC 2	–	1,035	–	–

SCT — sympathetic cervical trunk, DC — denervated control.

*Additional phasic burst of activity at late inspiration and early expiration.

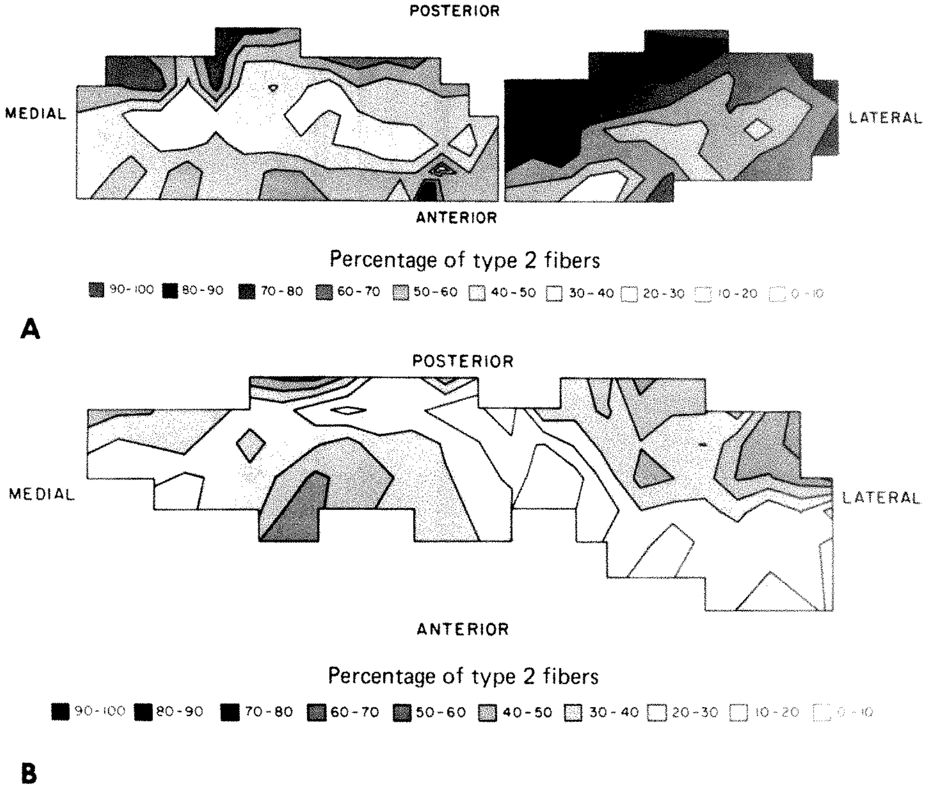


Fig 4. Contour analyses of type 2 fiber frequency in cross sections of right posterior cricoarytenoid muscles. A) Normal muscle. Note high percentage of type 2 fibers in lateral region. B) Reinnervated muscle. Note lower overall percentage of type 2 fibers than in A.

dom mosaic pattern (Fig 3B). In contrast, two of the four reinnervated muscle specimens demonstrated "fiber type grouping," with large clusters of type 2 fibers adjacent to smaller clusters of type 1 fibers (Fig 3C). In these two reinnervated specimens, the "fiber type grouping" pattern is located in the lateral region of the muscle. A PAS stain of these two specimens revealed glycogen depletion in the same region (Figs 5 and 6). The denervated muscle demonstrated neither "fiber type grouping" nor glycogen depletion (Fig 3A).

DISCUSSION

This experiment has demonstrated the successful reinnervation of the PCA muscle after the direct implantation of the SCT. This conclusion is supported by the following findings:

1. Spontaneous oscillatory motion of the reinnervated vocal cord and abduction during hyperpnea.
2. Tonic and phasic EMG activity in the reinnervated muscles, both of which were abolished by sectioning of the SCT nerve.
3. Greater number of normal-size muscle fibers than in the denervated controls.
4. ATPase staining showing classic "fiber type grouping" with a predominance of type 1 fibers.
5. Prolonged electrical stimulation of the SCT producing glycogen depletion in clusters corresponding to the regions of "fiber type grouping."
6. Electrical stimulation of the nerve eliciting visible PCA muscle contraction as well as vocal cord abduction in all reinnervated dogs. This effect is abolished when the nerve is transected.

The last two findings are the most convincing evidence for reinnervation. Large clusters of muscle fibers became glycogen-depleted after electrical stimulation. Glycogen depletion demonstrates the presence and precise arrangement of reinnervated fibers.[42] Second, the contraction of the PCA muscle after electrical stimulation of the SCT is conclusive proof of reinnervation. The denervated muscle did not respond even to higher voltages of stimulation.

The predominance of type 1 (slow-twitch) fibers agrees with findings of the only previous histochemical study of sympathetic reinnervation. Ramirez and Luco[31] found that the SCT-reinnervated cricothyroid muscle has a slower contraction time as well as an enzyme profile characteristic of slow muscle. In contrast, PCA muscle reinnervation with a somatic motor nerve, such as the RLN, results in almost equal groups of both type 1 and type 2 fibers in a classic "type-grouping pattern."[43] This pattern contrasts with the random mosaic appearance of fiber types in normal muscle.[44]

Since the SCT reinnervated the PCA muscle, it was expected that the muscle's movement would reflect the activity of the SCT. There were two types of activity recorded in the EMG of the reinnervated muscles. First, there was tonic activity at about 2 to 3 Hz that was present in all four dogs and did not vary with respiration. This tonic EMG activity correlated with the observed oscillatory vocal cord motion in all four dogs. This was the first time that a

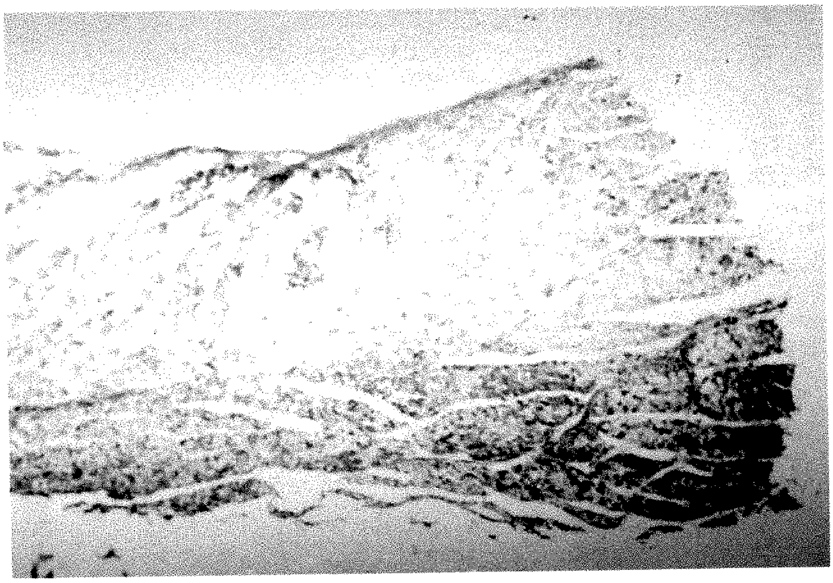


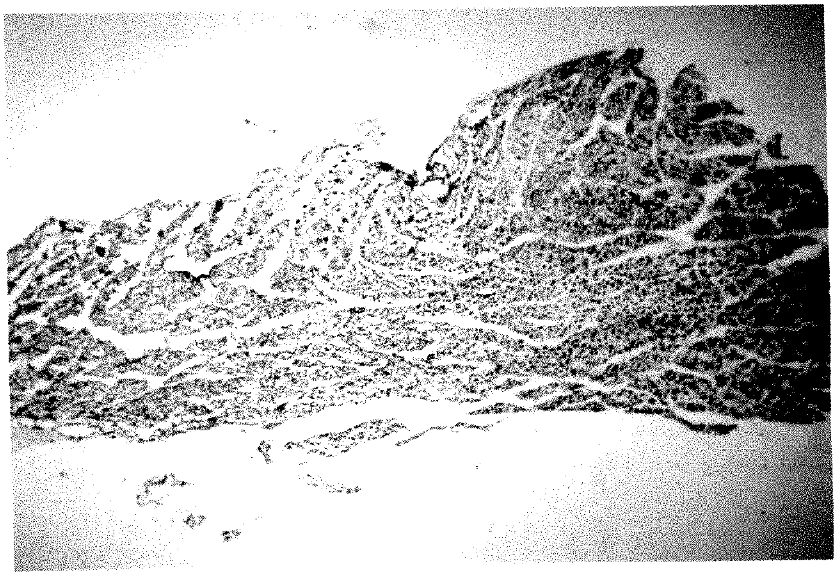
Fig 5. PAS reagent glycogen stain of transverse section of entire PCA muscle (original x10). Note large area of glycogen-depleted fibers in upper right (lateral region). In medial region (left), muscle's cross-sectional width is reduced because of fiber atrophy.

sympathetic nerve had been observed to cause spontaneous motion of a striated muscle.

The second type of EMG activity, seen in only two of the four dogs, was a phasic burst that occurred at late inspiration and extended into early expiration. This activity was not synchronous with that of the opposite PCA muscle and disappeared after cutting of the SCT. This agrees with the findings of previous investigators who found that maximal sympathetic discharge, in dogs, occurs during expiration.[45,46] Clearly, the EMG activity originated in the SCT. However, it is unclear whether this activity was capable of abducting the vocal cord. In the two dogs that had this phasic EMG activity, abduction was not seen simultaneously. Instead, in all four dogs abduction occurred synchronously with the opposite vocal cord during hyperpnea. This pattern of abduction was seen by Crumley et al[17] in dogs unsuccessfully reinnervated with the sternothyroid NMP. They theorized that the slight abduction reflected the activity of the cricothyroid or accessory muscles of respiration. In retrospect, it would have been advantageous to section the superior layngeal nerve and the ansa cervicalis to abolish the aforementioned activity. Therefore, it cannot be concluded with certainty that the SCT was able to abduct the vocal cord through its own activity.

The reason that the bursts of EMG activity did not cause obvious vocal cord abduction may be related to the technical problems of nerve implantation. In the experiment the PCA muscle was undermined off the cricoid cartilage before the nerve was implanted. This causes surgical scarring that will restrict motion. Second, nerve implantation may result in only partial reinnervation, because the nerve is not in contact with the maximum number of motor end plates. Gruber[47] found that direct vagal implantation reinnervated only a small percentage of motor end plates in the sternohyoid mus-

Fig 6. ATPase stain of specimen in Fig 4B (original x10). Note number of type 1 (dark) fibers in lateral (right) region.



cle. Indeed, in this experiment histologic evidence of reinnervation was confined largely to the lateral region of the PCA muscle. Perhaps a direct neural anastomosis of the SCT to the cut end of the abductor branch of the RLN might reinnervate a much larger portion of the PCA muscle without surgical scarring.

Another important aspect of this experiment is the anesthesia technique. Sympathetic discharge is very sensitive to physiologic and pharmacologic manipulations. It is well known that blood pressure fluctuations will alter sympathetic discharge via the baroreceptor reflex.[48] In addition, high doses of barbiturate anesthetic often will suppress sympathetic neurons.[49] It would be advantageous to study the reinnervated PCA muscle's motion under controlled physiologic conditions such as with an inhalation anesthetic and an arterial line. In addition, pharmacologically induced hypotension could activate the sympathetic system to produce a more pronounced response.

Despite these shortcomings, this experiment has demonstrated the successful reinnervation of the PCA muscle with the SCT. This was documented by histology, EMG, and glycogen depletion, as well as contraction in response to electrical stimulation. In addition, the reinnervated PCA muscle demonstrated active tonic motion.

With technical refinement it should be possible to achieve useful motion in an SCT-reinnervated larynx. Although the timing of sympathetic activity in the dog is not optimal, the human SCT is known to have its greatest activity during early inspiration.[36] Therefore, SCT reinnervation may benefit patients with BVCP. On the other hand, if tonic motion is all that is possible, then SCT reinnervation may be better suited for tonically active muscles. These include the laryngeal adductors in cases of unilateral vocal cord paralysis and the muscles of facial expression in cases of facial nerve paralysis. Furthermore, SCT reinnervation also may be useful for laryngeal pacing, because reinnervated muscle is much more sensitive to electrical stimulation than denervated muscle.[50] Overall, laryngeal autonomic reinnervation is promising and deserves further investigation for all of its potential applications.

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REQUEST FOR PROPOSALS
AMERICAN LARYNGOLOGICAL ASSOCIATION

The American Laryngological Association has established a grant for research on laryngology, rhinology, and related subjects. The maximum grant for one year is $15,000. Deadline for submission is June 1, 1990. For the specifics of eligibility and application materials, write to the American Laryngological Association, H. Bryan Neel III, MD, Secretary, 200 First Street, SW, Rochester, MN 55905.

Ann Otol Rhinol Laryngol 99:1990

USE OF NASAL VALVE STENT WITH ANTERIOR RHINOMANOMETRY TO QUANTITATE NASAL VALVE OBSTRUCTION

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Some patients have increased resistance in the nasal valve area that is static and does not collapse. Anterior rhinomanometry is unable to document nasal valve disorders in these instances. A simple stent was devised to open the nasal valve area during anterior mask rhinomanometry. Three groups of subjects were studied with and without the stent. These groups were 1) patients with anatomic findings of nasal valve obstruction, 2) normal control subjects, and 3) normal control subjects with artificially created midseptal nasal obstructions. At peak inspiration the median decrease in resistance with the stent in place when compared to nonstented values was 0.91 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ for group 1, 0.27 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ for group 2, and 0.25 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ for group 3. Comparisons using the nonparametric Wilcoxon test had a significance level of $p < .001$. An easily fashioned, well-tolerated nasal valve stent can be readily incorporated in anterior mask rhinomanometry technique. With use of the stent, nasal valve obstruction can be accurately diagnosed and quantitated.

KEY WORDS — nasal airway, nasal obstruction, nasal resistance, nasal stent, nasal valve, nose.

INTRODUCTION

The nasal valve area is bounded by the caudal end of the upper lateral cartilage and the nasal septum. Deformities in this area may significantly contribute to nasal obstruction. Physical examination plays an important role in the diagnosis of nasal valve disorders.[1] However, physical diagnosis provides no permanent record of the degree of airway obstruction, nor is it able to quantitate the extent of this obstruction.

Rhinomanometry allows for objective quantitation and recording of airway resistance. Marked differences between inspiratory and expiratory nasal resistance can be attributed to narrowing of the nasal valve area.[2,3] To diagnose nasal valve obstruction, anterior mask rhinomanometric pressure-flow curves are analyzed to determine the transmural closing pressures for that nasal passage. When this critical transmural pressure is reached, the nasal valve can act as a Starling resistor and collapse, resulting in a plateauing of the pressure-flow curve.[4]

In our experience some patients have increased resistance in the nasal valve area, which is static and does not collapse. The pressure-flow curves in these patients document increased resistance, but no anatomic site can be inferred from analysis of the curve. When rhinomanometry is performed with use of a "head-out" body plethysmograph, manipulation of the patient's nasal vestibule and valve area can easily be performed with a splint.[5] However, when anterior mask rhinomanometry is performed, manipulation by the tester cannot be done. To address this, a stent was devised that could be inserted within the nasal vestibule prior to mask placement, to hold the nasal valve area open during testing. To further assess the ability of this method to differentiate nasal valve obstruction from obstructions occurring more posteriorly in the nasal cavity, fiberfoam pledgets were used to create midseptal obstructions simulating septal deviations. This material has proven useful in simulating anatomic obstructions within the nasal cavity.[6,7]

METHODS

Three groups of patients were studied with and without the stent. The first group consisted of patients with nasal valve disorders. These patients had complaints of nasal obstruction, and the diagnosis of nasal valve disorder was supported by physical examination including the Cottle maneuver. Patient ages ranged from 26 to 53; three were women and two were men. Three of these patients had prior nasal operations, and two had a history of nasal trauma. One patient with a prior nasal operation also had Ehlers-Danlos syndrome. One posttrauma patient had only unilateral obstruction.

Five normal control subjects were selected from the residents and staff of the otolaryngology clinic. There were three women and two men with ages ranging from 26 to 32. These subjects had no complaints of nasal obstruction and no previous nasal trauma or nasal operations. Examination revealed no significant nasal deformity or disorder.

The third group was comprised of the same control subjects with pieces of expanded fiberfoam inserted into the nasal cavity in the midseptal region at approximately the junction of the quadrangular cartilage and the ethmoid bone. This area is also described as the turbinate or area 4 region.[4] Dimensions of the expanded fiberfoam pledgets were approximately 30 x 5 x 10 mm. The actual dimensions of the fiberfoam within the nasal cavity

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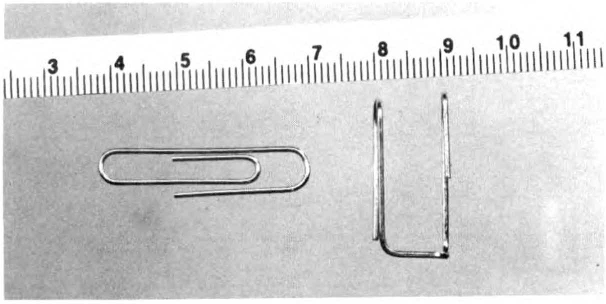

Fig 1. Nasal stent fashioned from paper clip. Width between "arms" is 1 cm. Scale is in centimeters.

varied, as the fiberfoam conformed to the shapes of the individual nasal passages.

A Rhinotest MP anterior mask rhinomanometer was used (IC Intertronics, Inc, Spring Valley, Calif). This unit measures airflow in cubic centimeters per second, and pressure in pascals. The nasal stent was fashioned from a midsized paper clip as depicted in Fig 1. The dimensions of the stent were standardized at 1 cm in width. Care was taken to bend the stent by hand, since an instrument might have left burs that could injure the nasal mucosa or vestibular skin. The pressure transducer was connected to the nasal vestibule of the nontest-side nasal passage by the use of plastic tubing affixed to Microfoam tape as depicted in Fig 2. This method of connecting the tubing to the nose was shown to the senior author by T. V. McCaffrey of the Mayo Clinic. All subjects were first decongested with 0.5% phenylephrine hydrochloride spray. After 10 minutes, pressure-flow curves were obtained for both nostrils. The sample gathering period lasted 10 to 15 seconds, during which the subjects took four to five normal respirations. Next, the stent was placed between the nasal septum and the caudal end of the upper lateral cartilage to dilate the nasal valve area as depicted in Fig 3. Pressure-flow curves were then obtained for each stented nostril.

All resistance values were calculated at peak inspiration on the pressure-flow curve. Each value represents the resistance in one nasal passage. Therefore, for the control and midseptal obstruction groups, $n = 10$. Since one nasal valve patient manifested unilateral obstruction, $n = 9$ for this group.

RESULTS

The median nasal airway resistances at peak inspiration for the unstented nasal valve patients and midseptum subjects were essentially similar (1.12 versus 1.17 $Pa \cdot cm^{-3} \cdot s^{-1}$), while the unstented control subjects had markedly less nasal resistance (0.39 $Pa \cdot cm^{-3} \cdot s^{-1}$) (see Table and Fig 4). However, in the stented trials, the nasal valve patients and control subjects had similar resistance values (0.15 and 0.17 $Pa \cdot cm^{-3} \cdot s^{-1}$), while the subjects with midseptum obstruction had, by comparison, a much higher median value for airway resistance (0.79 $Pa \cdot cm^{-3} \cdot s^{-1}$).

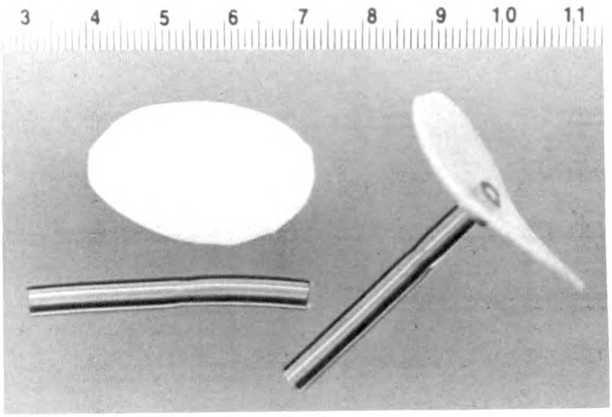

Fig 2. Pressure transducer tubing. Microfoam tape is used to create seal over nostril. Scale is in centimeters.

The median decrease in airway resistance after stent placement was marked in the nasal valve patients, while the control subjects and midseptal obstruction subjects had essentially the same small decrease in resistance, as depicted in the Table and in Fig 5.

Simultaneous one-sided comparisons of the change in resistance of the nasal valve patients with the control and midseptal obstruction groups using the nonparametric Wilcoxon test showed the nasal valve group median decrease in resistance to be larger than that for the other two groups at a level of significance $p < .001$.

DISCUSSION

Anterior mask rhinomanometry has proven itself to be a reliable, reproducible assessment of nasal resistance. However, since the mask must be worn during the data collection, manipulation of the anterior part of the nose is hampered. In order for a stent to be fitted and stay in place during the data collection, it must be light and have some intrinsic

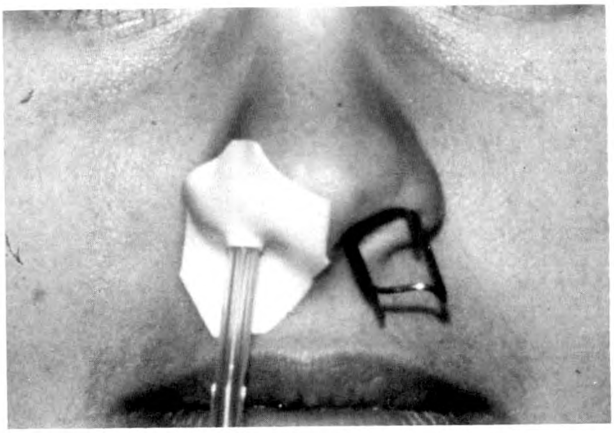

Fig 3. Nasal valve stent and pressure transducer tubing in place ready for mask positioning.

NASAL AIRWAY RESISTANCE AT PEAK INSPIRATION

	Unstented	*Stented*	*Decrease in Resistance*
Nasal valve disorder (n = 9)	1.12 (0.69-3.96)	0.15 (0.06-0.28)	0.91 (0.61-3.73)
Control (n = 10)	0.39 (0.21-0.61)	0.17 (0.09-0.36)	0.27 (0.01-0.56)
Midseptal obstruction (n = 10)	1.17 (0.43-4.75)	0.79 (0.16-4.32)	0.25 (0.08-0.43)

Values are median resistance with range in parentheses. Each represents single nasal passage measured in $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ ($p < .001$).

spring. It must also have a small enough area so as not to significantly contribute turbulence to the airflow, increasing the resistance. A simple paper clip solved this problem. It is malleable and easily bent by hand, and is able to be compressed slightly while being fitted in the nose, but springs back to the desired dimension. Once in place, it usually stays in place during the testing procedure. A standard width was used to obtain consistent results. The width of 1 cm was chosen because it was a value that could dilate most nasal valves yet fit within the dimensions of the nasal vestibule. Obviously, the midportion of the stent contributes some resistance to the airflow. However, since the stent's dimensions are uniform, its contribution to nasal resistance should be constant from patient to patient. The stent dilates the nasal valve so that the net effect is to markedly reduce nasal airway resistance (Fig 4). Thus, any turbulence created by the stent appears to be constant and negligible, and does not influence overall results and conclusions.

To further assess the ability of this stent to differentiate nasal valve disorders from nasal obstruction in other areas, a midseptal area obstruction was also analyzed. In order to avoid the difficulty of finding a uniform population of subjects with isolated midseptal nasal obstructions, artificial midseptal obstructions were created in the control population with use of expanded fiberfoam material. This method has been documented as an adequate substitute for an anatomic deformity.[6,7] With this method and using normal controls, one can be certain of the location of the elevated resistance.

The stenting method is able to demonstrate a marked decrease in nasal airway resistance of nasal valve patients compared to unstented values and compared to stented control and midseptal obstruction subjects. Furthermore, the decrease in resistance of all 20 values measured in the control and midseptal groups ranked entirely below the 9 resistance decrease values measured in the nasal valve group. In other words, in no instance did the decrease in resistance in the stented control or midseptal obstruction subjects exceed 0.6 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$, and in no instance was the decrease in resistance for the stented nasal valve patients less than 0.6 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$. This strongly suggests a minimal degree of total population overlap and hence a means for discriminating nasal valve obstruction that has both high specificity and high sensitivity.

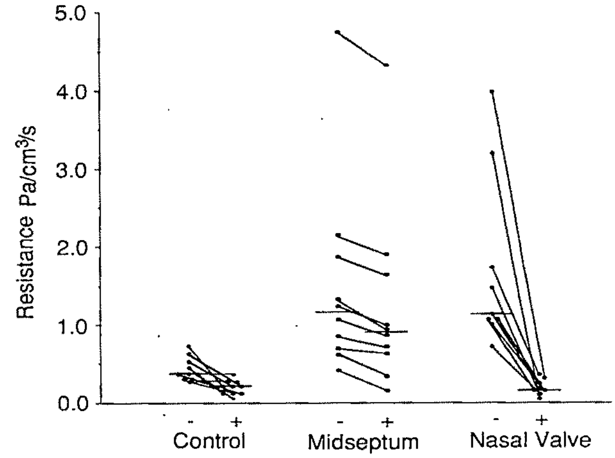

Fig 4. Nasal airway resistance at peak inspiration before and after nasal valve stent placement in control subjects (Control), control subjects with expanded fiberfoam placed in midseptal area (Midseptum), and patients with nasal valve disorders (Nasal Valve). Each point represents resistance calculated from single nasal passage. Slashes — median values, minus — without stent, plus — with stent.

In none of the stented normal control subjects or nasal valve patients was the resistance of a nasal passage greater than 0.4 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$. This suggests an upper limit to the normal range. Larger studies will be needed to confirm this observation.

Some patients may exhibit stenosis of the nasal vestibule or valve area rather than collapse or narrowing. This may inhibit the ability of the stent to dilate the area, thereby impairing the stent's ability to fully quantitate the nasal valve's contribution to nasal resistance. Significant stenosis could even prevent stent insertion. However, physical examination should identify these patients.

In addition to dilating the nasal valve area, the stent also opens the nasal vestibule area. The stent cannot isolate nasal valve from nasal vestibule dis-

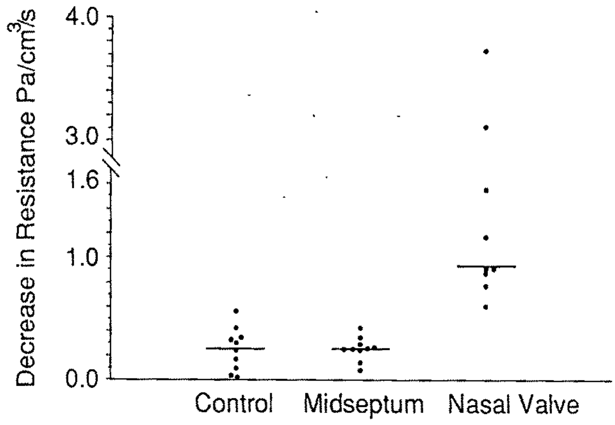

Fig 5. Change in nasal airway resistance produced by stenting nasal valve in control subjects (Control), subjects with expanded fiberfoam placed in midseptal area (Midseptum), and patients with nasal valve disorders (Nasal Valve). Slashes — median values.

orders. This is not of clinical significance for two reasons. First, since the nasal valve area has the smallest cross-sectional area of the nasal passageway, it develops the greatest drop in pressure due to Bernoulli's law and is thus the area to act most significantly as a Starling resistor.[6] Second, should the nasal vestibule contribute significantly to airway obstruction, either through stenosis or collapse, the anatomic deformity would be readily apparent on physical examination. Obviously, the nasal vestibule and nasal valve area are contiguous structures, and collapse cannot occur in one area without affecting the other area to some degree. Almost always, it is the septum and upper lateral cartilages that provide the critical support for the anterior nasal passage. Therefore, the nasal valve area has been the focus of this study.

The stent placement should be observed throughout the entire rhinomanometric measurement, as dislodgement could occur while placing the mask or from patient movement. This would reduce stent effectiveness and adversely influence results.

The nasal stent provides a method of quantitating the contribution to nasal resistance provided by a nasal valve disorder. It is most valuable in documenting nasal valve obstruction in patients with relatively stiff anterior nasal support that does not collapse at a certain transmural pressure. In the nasal valve group, three patients demonstrated the classic plateauing of the curve once a critical transmural pressure had been reached. However, two patients did not display this plateau. Their nonstented rhinomanometric curve was similar to a fixed, more posterior obstruction in that their peak inspiratory and expiratory airway resistance values were approximately equal. This obstruction completely reversed with the stent, thereby documenting the anterior nature of these patients' disorders.

Resistance values at a given radius, pressure, or flow can be compared.[8,9] Analysis of the data at given radii also demonstrated the same trend, but the resistance at peak inspiration was chosen because it allowed for the most significant and easily compared data. The use of resistance at peak inspiration is a valid method for comparing changes in overall nasal resistance.[10]

In summary, an easily fashioned, well-tolerated nasal stent can be readily incorporated in anterior mask rhinomanometry technique. With the stent, nasal valve disorders can be diagnosed when the resistance drops more than 0.6 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ in a nasal passage. When the stent is in place, nasal airway resistance of less than 0.4 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ suggests normal resistance in the cavernous area. Stented nasal resistance of greater than 0.4 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ and a change in resistance of less than 0.6 $\mathrm{Pa \cdot cm^{-3} \cdot s^{-1}}$ would suggest obstruction posterior to the vestibule and nasal valve area. The nasal stent in anterior mask rhinomanometry provides a highly specific and sensitive method for the diagnosis and quantitation of nasal valve obstruction.

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APPROACH FOR OXYGENATION OF THE NEWBORN WITH AIRWAY OBSTRUCTION DUE TO A CERVICAL MASS

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Large congenital cervical neck masses present major difficulties in management of the neonatal airway at delivery and in the perinatal period. With ultrasound, these lesions can be predicted prenatally. An airway treatment plan can then be formulated and modified in relation to the airway presentation at birth. We describe a case of a massive cervical-mediastinal teratoma and our management plan. Preparation involved a multidisciplinary approach including endoscopy to secure the airway while the neonate remained on fetal circulation and an extracorporeal membrane oxygenation system was available. Once the infant's condition was stable, a cervical approach with resection of the massive teratoma with mediastinal dissection without sternotomy was successful. A differential diagnosis of cervical neck masses and review of cervical teratomas is presented.

KEY WORDS — airway obstruction, extracorporeal membrane oxygenation, teratoma.

Advances in prenatal diagnosis, with the aid of ultrasound, have increased the chance for survival in neonatal airway obstruction. If a major upper-airway obstruction is anticipated, a management plan ensuring oxygenation of the neonate can be employed.

We describe a case involving a prenatally diagnosed large cervical teratoma. A management team was developed to handle the airway. First, an elective cesarean section was performed. The team consisted of an otolaryngologist, a neonatologist, a pediatric surgeon, an obstetrician, and nursing personnel. Neonatal bronchoscopes, laryngoscopes, and endotracheal tubes and a tracheostomy tray were prepared for use. An extracorporeal membrane oxygenation (ECMO) system was also present.

This management plan allows for resolution of difficulties in securing an airway. Large cervical masses or upper-airway anomalies may present major anatomic variations and make endoscopic airway control or tracheostomy impossible. The use of ECMO can provide temporary blood oxygenation while immediate neck exploration for an airway proceeds.

CASE REPORT

A 26-year-old woman was noted to have polyhydramnios. Ultrasound also revealed a large right fetal neck mass (see Figure, A). No other fetal abnormalities were noted.

Consultations were obtained with otolaryngology and pediatric surgery departments, and a planned cesarean section was advised. Depending upon airway presentation, the child would remain on placental circulation as the airway was secured. First, endoscopy would be attempted; but if an adequate airway could not be secured, tracheostomy would not be a sound alternative, because the neck mass might obscure and distort the trachea. As an alternative method of establishing neonatal oxygenation, a pediatric surgeon was consulted for placement of ECMO catheters. This ECMO system would vary from the standard neonatal venoarterial approach in two major respects. First, the umbilical arteries would serve as cannulation sites, since the carotid and jugular veins might be inaccessible. Second, the circuit would maintain fetal hemodynamic flow with oxygenated blood entering the vena cava via the umbilical vein. If ECMO was necessary, neck exploration with resection of the right neck mass and establishment of an airway would be performed at the time of delivery.

At 36 weeks' gestation, the mother went into labor. Pharmacologic attempts to abort labor were unsuccessful. An amniocentesis performed several days earlier revealed an immature lecithin-sphingomyelin ratio. A cesarean section was performed. The baby was paralyzed with succinylcholine to prevent spontaneous ventilation. Thus, we maintained fetal circulation with a patent ductus arteriosus. While the child relied on fetal circulation, direct laryngoscopy was performed, revealing a normally developed larynx severely deviated to the left. With some difficulty secondary to tracheal deviation, a 3.0-mm endotracheal tube was inserted into the trachea, and the child was ventilated. Simultaneously with endoscopy, dissection of the umbilical vessels was accomplished and catheters for ECMO were inserted, but the catheters were removed when the airway was secured and neonatal oxygenation was ensured. The infant was then transferred to the intensive care nursery.

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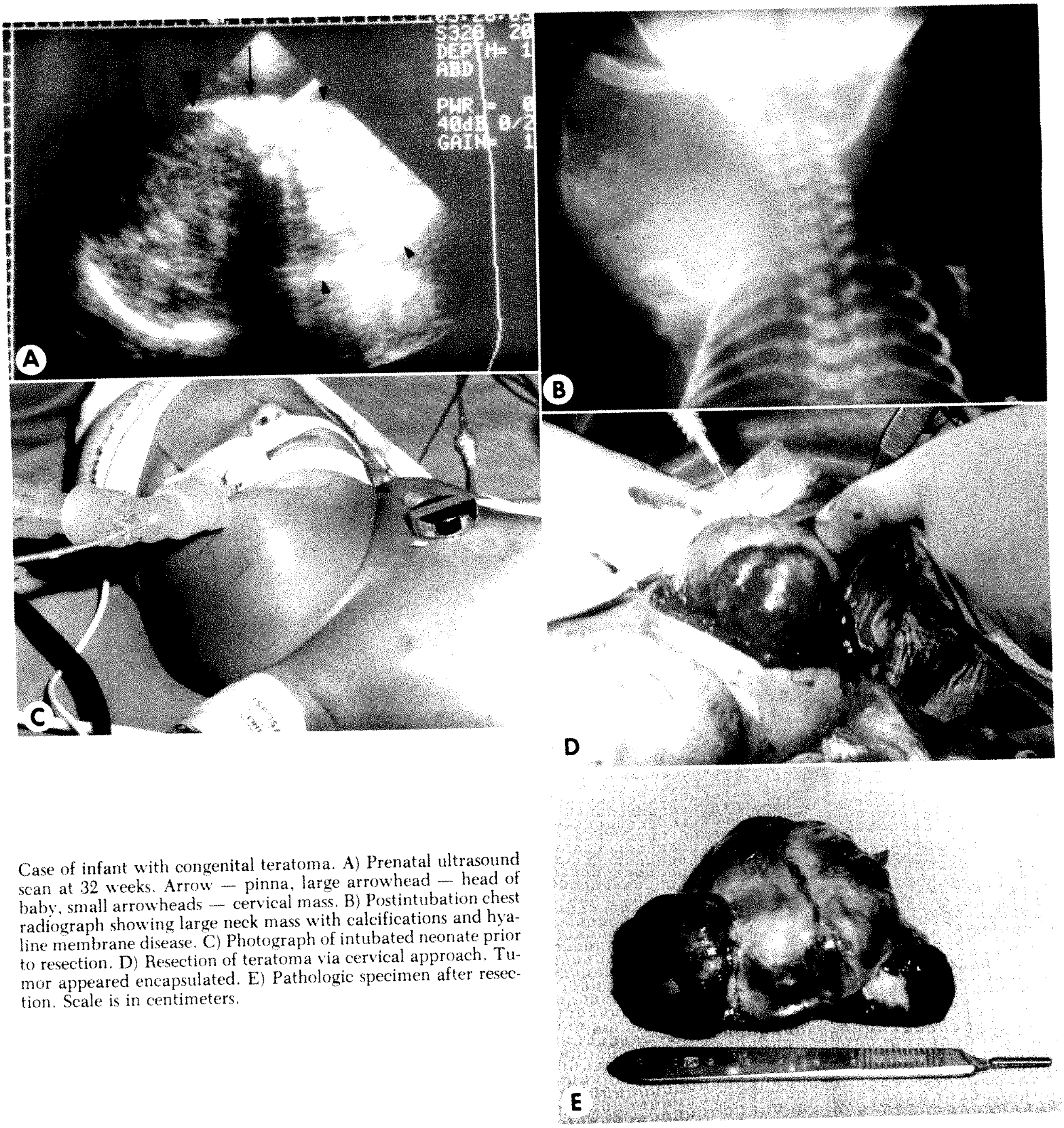

Case of infant with congenital teratoma. A) Prenatal ultrasound scan at 32 weeks. Arrow — pinna, large arrowhead — head of baby, small arrowheads — cervical mass. B) Postintubation chest radiograph showing large neck mass with calcifications and hyaline membrane disease. C) Photograph of intubated neonate prior to resection. D) Resection of teratoma via cervical approach. Tumor appeared encapsulated. E) Pathologic specimen after resection. Scale is in centimeters.

Postnatal chest radiography revealed hyaline membrane disease (see Figure, B). The neck mass appeared to extend below the carina and contained several calcifications. Attempts to improve pulmonary status were unsuccessful, and high ventilator settings were required to maintain adequate gas exchange. A computed tomographic scan of the neck and thorax revealed a probable teratoma extending from the right side of the skull base to the carina. Resection of the mass was then performed 5 days after birth.

The resection was approached via an extended apron cervical incision. The mass appeared to be well encapsulated and was not adherent to major structures. Dissection proceeded from the skull base down the carotid sheath, preserving all major neural and vascular structures (see Figure, D). The mass encircled the anterior larynx and trachea, but a plane of dissection was evident. The inferior extent was just below the carina, and the mass displaced the right lung apex. Mediastinal dissection was possible through the cervical approach, and sternotomy was not required. After resection, laryngoscopy and bronchoscopy were performed, and the airway appeared intact.

Postoperatively, the child had an uneventful course, and he was extubated on the ninth postoperative day. He had no major airway problems after extubation. Both vocal cords were mobile. He was discharged breathing, eating, and crying normally.

He is presently 14 months of age and has no sequelae from the operation. He is normal for age in height, weight, and development.

The pathologic examination revealed a 12 x 10 x 6-cm mass with cystic elements, cartilage, and bone evident (see Figure, E). Microscopic sections showed mature and immature teratoma elements with no germ cell elements.

DISCUSSION

Polyhydramnios occurs in 0.41% of pregnancies. Diagnosis of congenital malformations occurs in about 20% of these cases.[1] Obstruction of the upper aerodigestive tract can produce polyhydramnios. Hypoplastic craniofacial syndromes may be predicted prenatally by use of ultrasound, as well as associated cardiac and central nervous system anomalies. Esophageal atresia may be difficult to diagnose, as it is often associated with tracheoesophageal fistula, thus producing little obstruction. Neck masses are a rare source of polyhydramnios overall.[2]

Differential diagnosis of cervical masses that could produce neonatal airway obstruction include cystic hygroma (most common), hemangioma, branchial cleft cyst, congenital goiter, teratoma, and laryngocele.[3] Prenatal ultrasound can be useful in predicting the lesion as well as the degree of potential airway obstruction.[4] Other congenital cervical masses, less likely to cause airway obstruction, are thyroglossal duct cysts, neurogenic tumors, and esophageal diverticula.

Cervical Teratoma. Congenital cervical teratomas present with polyhydramnios in 20% of cases. Cervical teratomas occur mostly in infants and are rarely malignant in this population. A review of over 150 cases of cervical neonatal teratomas revealed lymph node metastasis in two patients.[5-7] Nine cases of cervical teratoma are reported in adults, six of which were malignant. Cervical teratoma accounts for less than 5% of all teratomas.[8]

Cervical teratomas often present as midline or paramedian structures. Previous classification was based on association with the thyroid gland and vessels, although more recent literature has abandoned this system. They are irregular in shape and tend to be firm in consistency, with some cystic areas. The overlying skin is usually mobile. They are often in close proximity to the larynx and trachea.[3]

Computed tomographic scans can be diagnostic of teratomas. About 50% of tumors are calcified, and occasional cystic elements with adjacent cartilage and bone can confirm the diagnosis. Computed tomographic scanning of the neck and thorax should be performed if possible prior to operation to evaluate mediastinal extension and impingement on the trachea and bronchi.

Historically, large cervical teratomas have presented as stillbirths in about 17% of cases.[9] Premature delivery is also common. The presence of other congenital anomalies is rare. Living infants present with airway obstruction. Early operation is advised to avoid airway collapse; operative mortality is 9%.[9] Postoperatively, death secondary to aspiration has been noted.[10] This may be related to vagus nerve dysfunction with vocal cord paresis. The larynx should be assessed prior to extubation to ensure glottic competence.

Histologic examination reveals teratomas to contain elements from all three germ cell layers. There are variable degrees of maturation present, but cervical neonatal teratomas rarely contain embryonal components with malignant behavior. Complete resection is curative, although long-term follow-up is advised.[11]

Extracorporeal Membrane Oxygenation. Extracorporeal membrane oxygenation has been successfully used since 1975 for neonates having severe respiratory and/or cardiac failure.[12] Cannulation of the right atrium and aortic arch is normally achieved via the right internal jugular vein and carotid artery. High flow is generally required for tissue oxygenation and perfusion; catheters must be able to shunt up to 80% of cardiac output through the ECMO circuit.[13]

Extracorporeal membrane oxygenation has not been previously reported as used in cases of congenital airway obstruction. Application of ECMO to large cervical masses would preclude rapid access to the jugular vein and carotid artery. It was hoped that at the time of delivery, if an airway could not be readily established, the umbilical vessels could serve as cannulation sites. Unfortunately, the umbilical vessels are too small to accommodate the usual-size catheters needed for sufficient flow. Knowing that this modified ECMO might not be capable of high-volume oxygen exchange and shunting, we decided to try to establish ECMO with a fetal hemodynamic circuit. Prior to birth, the P_{O_2} of the baby may be 35 to 40 mm Hg in arterial blood. It is hoped that this ECMO circuit would maintain or improve this arterial P_{O_2}. This is why the neonate was paralyzed prior to delivery so that no spontaneous respiration would occur and alter the fetal hemodynamics. In the case presented, cannulas were introduced via the umbilical vessels, and the arterial cannula would serve as the afferent limb (reversed from conventional ECMO). The airway was secured prior to initiating the described ECMO circuit, so at present this method remains unproven. This low-flow placental-circulation ECMO circuit has not been described or reported as successfully used in humans. Extracorporeal membrane oxygenation requires systemic heparinization, and this would increase chances of major bleeding if resection of an obstructing cervical mass was necessary.

CONCLUSIONS

Severe airway obstruction may be diagnosed prenatally. An airway management team can then be assembled and increase the chance of adequate oxygenation of neonates after delivery. Large cervical masses that in the past might have accounted for stillbirths or perinatal asphyxiation can be resected, and previously unsalvageable lives can be saved. The use of ECMO may be applied to cases of upper aerodigestive tract hypoplasia or atresia and allow for time to secure or create an adequate airway. Expertise of and cooperation among the obstetrician, pediatric surgeon, neonatologist, radiologist, and otolaryngologist are required.

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Ann Otol Rhinol Laryngol 99:1990

LARYNGEAL GRANULOMATOUS POLYP AFTER SHORT-TERM INTUBATION OF A CHILD

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It is well known that prolonged endotracheal intubation may result in formation of laryngeal granulomata. It is rare to find such lesions following short-term intubation. Furthermore, the virtual absence of such granulomata in children has been attributed to certain characteristics of the pediatric larynx. We report a 7-year-old child who developed a laryngeal granulomatous polyp following endotracheal intubation for less than 12 hours. A discussion of the incidence, pathogenesis, and treatment of this and other postintubation laryngeal lesions follows.

KEY WORDS — intubation granuloma.

INTRODUCTION

It is well established that prolonged endotracheal intubation may result in significant injury to the larynx and trachea. Laryngotracheal injury following short-term intubation is rare and has received less attention in the literature. Postintubation granuloma of the larynx is an unusual complication of short-term intubation that has been previously reported only in adults.[1] The following case represents, to the authors' knowledge, the first report of postintubation laryngeal granuloma occurring in a child.

CASE REPORT

A 7-year-old boy with no known medical illness or prior hospitalizations was brought to the emergency room of a community hospital on June 14, 1987, after experiencing a generalized tonic-clonic seizure at home. On initial assessment his respirations were noted to be irregular, and an arterial blood gas examination revealed a significant respiratory acidosis. He was nasotracheally intubated with a 5-mm cuffed Silastic endotracheal tube and given 100% oxygen by ambu bag. There was no reported difficulty or complication with intubation. Seizure activity was controlled by administration of intravenous diazepam. Following correction of the acidosis, he was maintained on 50% oxygen by T-piece overnight. Approximately 11 hours after admission, he was successfully extubated, and his respiratory status remained stable. He had no complaints of sore throat, dysphagia, or odynophagia, and hoarseness was not noted. After extensive evaluation a diagnosis of idiopathic epilepsy was made, and he was discharged 3 days later on a maintenance dosage of diphenylhydantoin (Dilantin).

Approximately 3 months following this episode, he was noted to have an acute onset of hoarseness and inspiratory stridor that became more pronounced when he was in the supine position. There was no history of gastroesophageal reflux symptoms. After pediatric evaluation a diagnosis of asthma was made, and he was treated with bronchodilators and steroids. Because there was minimal improvement in symptoms, the child was referred to the otolaryngology service at our institution. Flexible fiberoptic nasopharyngolaryngoscopy revealed a pedunculated polypoid mass on the posterior aspect of the left true vocal cord. It was estimated to be 1 cm in diameter and was seen to flop into the subglottic region with inhalation and out with exhalation. The patient subsequently underwent direct laryngoscopy and excision of the mass without complication. The specimen was identified pathologically as a pyogenic granuloma with focal ulceration and epithelial hyperplasia. Some epithelial atypia and dyskeratosis were noted and were felt to be reactive in nature.

Following the operation the child regained a normal voice, and follow-up nasopharyngolaryngoscopy at 6 months revealed a normal larynx.

DISCUSSION

As endotracheal intubation has become the standard of care for controlling the airway of patients requiring ventilatory assistance, recognition of significant associated injuries has increased. Laryngotracheal injury may occur from traumatic introduction of the tube, or more commonly as a result of the continued presence of the tube within the airway.[2] Consequences of traumatic intubation include pharyngeal or laryngeal hematoma, laceration, cricoarytenoid dislocation, and even vocal cord paralysis.[2-4] Indwelling endotracheal tubes have been shown to cause tissue damage at the areas of contact between the laryngeal mucosa and the tube. These areas include primarily the posterior cricoid and the vocal processes of the arytenoids.[5,6] Barton[6] out-

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lined the sequence of events in the pathogenesis of laryngeal granuloma as follows. The trauma of the tube against the vocal processes causes an abrasion that results in perichondritis. This is followed by secondary infection and ulceration. As this denuded area attempts to heal, a sessile granuloma forms. With continued proliferation of the central portion of the granuloma and simultaneous epithelialization of the margins of the lesion, a granulomatous polyp forms. Donnelly[7] has subsequently shown that 1) epithelial loss can occur following as little as 1 hour of intubation, 2) perichondritis of the vocal processes becomes increasingly frequent after 48 hours of intubation, 3) bacterial contamination of the ulcer is common after 24 hours, and 4) the inflammatory response that may culminate in granuloma formation follows extubation.

It has become clear that the degree of tissue damage as well as the incidence of complications increases with the duration of intubation, and much has been written concerning the consequences of prolonged intubation.[8-16] Relatively little attention has been given to the hazards of short-term intubation, partially because of a lack of consistency in defining short-term versus prolonged intubation.[11] That short-term intubation is not hazard-free is borne out by the fact that our patient's total intubation time was under 12 hours. This duration would not be considered excessive by most standards.

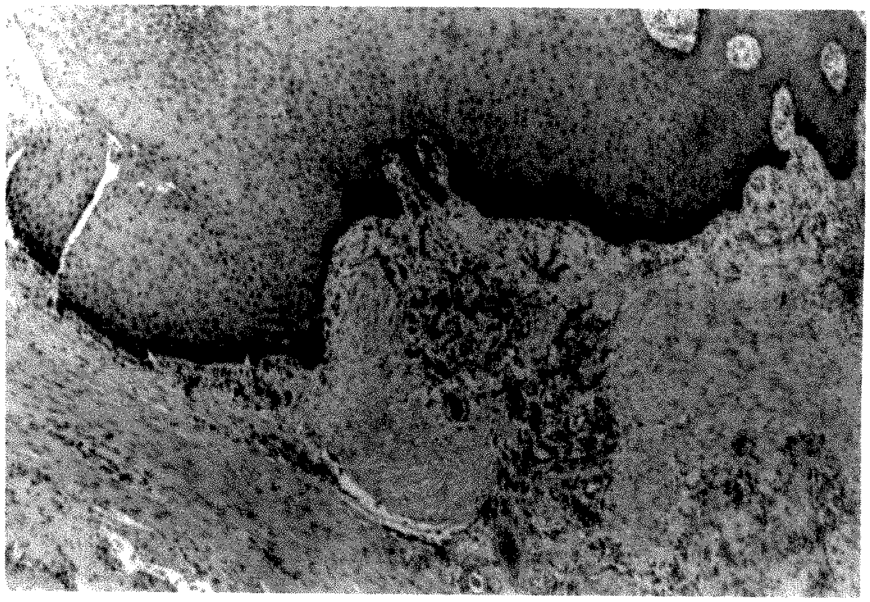
While laryngeal injury has been shown to occur with only brief periods of intubation and increase with a longer duration, such a clear correlation has not been shown with granuloma formation.[17] Because these lesions occur infrequently, it is likely that many are not recognized or not reported. Clausen[18] reported the first case in 1932, and by the 1950s, over 100 cases had appeared in the literature. There is a wide variation in the incidence among large series, but a reasonable estimate is 1 in 800 to 1 in 1,000.[19] In addition to the trauma of the endotracheal tube to the posterior larynx, other factors have been implicated in granuloma formation. These include abnormal head position or head movement during the operation, use of too large a tube, malpositioning or inappropriate pressure of the cuff, trauma during extubation, underlying infection, and gastroesophageal reflux.[1,5,6,20] Between 75% and 90% of cases reported have occurred in women, and several reasons for this female predilection have been proposed. Tonkin and Harrison[21] suggested that the size of the endotracheal tube relative to the dimensions of the larynx was larger in women, predisposing them to a greater degree of laryngeal injury and subsequent granuloma formation. Furthermore, the relatively thin mucosal layer covering the vocal process in women (59 μm versus 97 μm in men) offers little protection to the underlying perichondrium and results in more severe injury to this area.[1,20] In addition, women more frequently undergo operations requiring an abnormal head position, eg, thyroid operations.[19] These factors could account for the greater incidence of postintubation granuloma in adult women.

Up to now, the youngest patient reported to develop postintubation granuloma was 15 years of age.[22] Since the endotracheal tube takes up a large proportion of the glottic chink in children, one would suspect a high incidence of postintubation granuloma in this population. Several authors have attempted to explain the rarity of this lesion in children. Epstein and Winston[17] suggested that it could be accounted for by the infrequency with which children require intubation. This seems unlikely, considering the large number of tonsillectomies and adenoidectomies done in children. Another explanation is that the higher position of the pediatric larynx and its tapering shape may act to displace the mechanical forces toward the subglottic region.[1] These characteristics may confer a relative resistance to injury of the vocal processes and a relative predisposition to subglottic injury. This is consistent with clinical observations on the frequency of glottic and subglottic complications of intubation in children.

The case described here demonstrated several interesting features. First, this is the first report to the authors' knowledge of a postintubation granuloma occurring in a child. It is difficult to implicate the duration of intubation, traumatic introduction of the tube, or effect of head position as etiologic factors in this case, as none of these were excessive. One may speculate that the patient's seizure activity may have been accompanied by somewhat violent vocal cord adduction against the tube, resulting in more extensive damage.

Second, the history of abrupt onset of hoarseness and stridor at 3 months following extubation, with no intervening voice or respiratory complaints, is unusual. The most common symptom of laryngeal granuloma is hoarseness persisting beyond the immediate postoperative period. Foreign body sensation, chronic sore throat, and progressive dyspnea and stridor have also been noted. Our patient's symptoms were neither progressive nor persistent, and he was asymptomatic during the period of maturation of the granulomatous polyp. Since most granulomas heal without intervention, it is possible that these lesions do occur more frequently in children, but because they produce no symptoms and resolve spontaneously, they go unrecognized. Our feeling is that the pediatric larynx is vulnerable to intubation trauma and that postintubation granuloma does occur in this age group. In children especially, this diagnosis should be considered, as there is a very real potential for airway obstruction.

Third, our curiosity about this case was heightened by our pathologist's diagnosis of pyogenic



Section of postintubation granuloma of larynx showing characteristic radially oriented capillaries within stroma (H & E, original x100). Note also epithelial hyperplasia.

granuloma. This prompted us to review the specimen, which demonstrated features characteristic of postintubation granuloma and not pyogenic granuloma (see Figure). While the latter term has been used in the past to describe postintubation lesions of the larynx and trachea,[5,6] it has recently been shown to be a separate and distinct pathologic entity.[23] Specifically, postintubation granuloma consists of typical granulation tissue with capillaries oriented radially from the center of the lesion, and often covered with hyperplastic epithelium. Pyogenic granuloma, in contrast, is characterized by a lobular arrangement of capillaries similar to that seen in hemangioma. These lesions typically occur in the oral cavity, do not occur in the larynx or trachea, and are not related to intubation trauma.

CONCLUSIONS

1. Postintubation laryngeal granuloma can occur in children after uncomplicated short-term intubation.
2. Presenting signs and symptoms of this lesion in children may be different from the typical history in adults.
3. The otolaryngologist should include this entity in the differential diagnosis of vocal or respiratory symptoms in any patient who has been previously intubated.
4. Postintubation granuloma should not be misnamed pyogenic granuloma, as the latter lesion is not related to trauma and does not occur in the larynx or trachea.

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TONSILLECTOMY AND ADENOIDECTOMY: CHANGING TRENDS

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A review of 1,722 tonsil and adenoid procedures performed between 1978 and 1986 is presented. Each year there has been a progressive decrease in the number of procedures performed; the incidence of adenoidectomy has declined particularly. Although infection remains the predominant indication for surgery, there has been a dramatic rise in obstructive sleep apnea as a significant indication, from 0% in 1978 to 19% in 1986. At present, this trend promises to continue as physicians become increasingly aware of the prevalence and seriousness of adenotonsillar hypertrophy as a cause of sleep apnea, particularly in the general pediatric population.

KEY WORDS — adenoidectomy, sleep apnea, tonsillectomy.

INTRODUCTION

Perhaps no other surgical procedure has evoked more controversy over the past 50 years than the "simple" tonsillectomy and adenoidectomy, or "T&A." A 1957 critique[1] notes that "tonsillectomy has at some time been recommended for almost every disease of children and for many conditions, such as mental retardation or enuresis, which can hardly be called diseases." Apparently the controversy continues, since secondary enuresis[2,3] and asphyxic encephalopathy[4,5] have been shown recently to be potential manifestations of obstructive sleep apnea (OSA), a syndrome that is reversed by T&A in most children.[3,5-11]

Although recurrent infection has been, and remains, the predominant indication for surgery, OSA accounts for a continually increasing percentage of these procedures both in the United States[12] and Europe.[13,14] Awareness of a similar trend at our institution prompted a review of the indications for T&A surgery. The results are analyzed in historical perspective, with emphasis on the role of adenotonsillar hypertrophy in obstructive airway disease in the pediatric population.

METHODS

Review was performed of all tonsil and adenoid surgery at The Mount Sinai Medical Center between January 1978 and December 1986. The patient population was divided approximately equally between clinic and private referrals.

For each of the 1,722 procedures, the year, patient age and sex, type of operation, and admitting diagnoses were recorded. On the basis of the admitting diagnoses, the indication for each procedure was classified as either inflammatory (chronic recurrent tonsillitis or otitis media) or obstructive (sleep apnea); biopsies performed for suspected malignancy were excluded. No attempt was made to assess the severity of sleep apnea or the impact of T&A on disease; only the indication for surgery was of concern.

Diagnosis of OSA was restricted to patients with a typical history (loud continuous snoring with silent periods, restless sleep, mouth breathing) and confirmatory findings on physical examination (marked adenotonsillar hypertrophy). Preoperative consultation with a pediatrician was performed in all cases for medical clearance and confirmation of diagnosis. Sleep studies were not performed routinely, since the diagnosis was strongly supported by the history and physical examination, and polysomnography was not freely available during the study period. Presently, our main indication for polysomnography is to confirm a diagnosis of OSA in patients with a suggestive history but only mild to moderate adenotonsillar hypertrophy.

RESULTS

There has been a progressive decrease in the total number of procedures performed, from 282 in 1978 to 135 in 1986 (see Figure, A). The number of adenoidectomies, performed either alone or in combination with tonsillectomy, has declined particularly. The mean patient age has remained constant at 14 years, with no sex preference observed for the total number of procedures.

Infection was the major indication, responsible for 100% of the procedures in 1978, but only 81% in 1986. Tonsillectomy alone was the most commonly performed procedure for infection (see Figure, B). The mean patient age was 14 years, with no sex preference.

Obstruction has become an increasingly important indication for surgery, accounting for 0% in 1978 and 19% in 1986 (see Figure, C). In this group, T&A was the most commonly performed procedure (see Figure, D). The mean patient age was 6 years,

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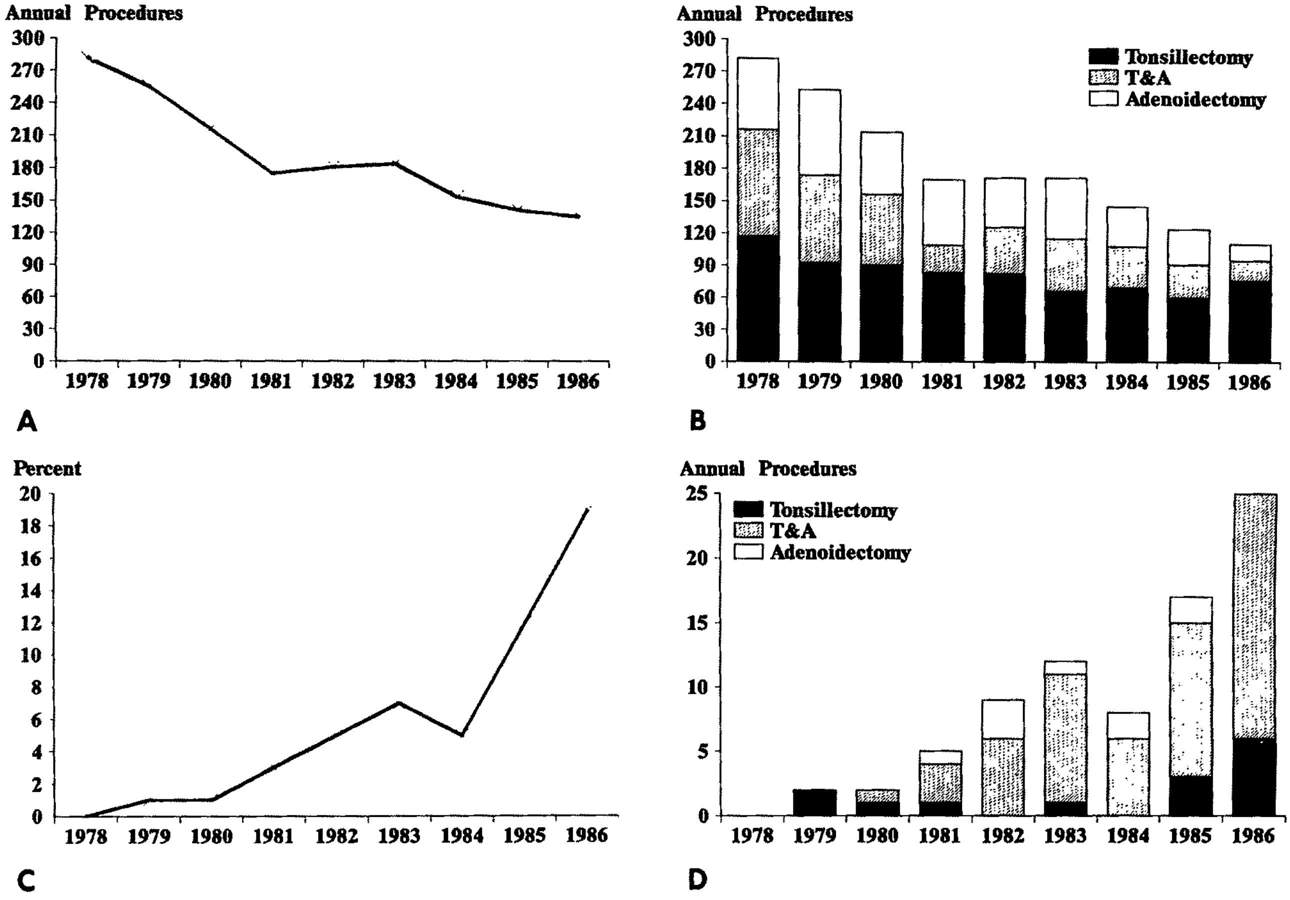
REPRINTS — Robert P. Green, MD, Dept of Otolaryngology, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.



Tonsil and adenoid procedures. A) Number of annual procedures. B) Breakdown of procedures performed for infection. C) Percentage of procedures performed for obstruction. D) Breakdown of procedures performed for obstruction.

with a male predominance of 3:2.

Since our interest was in surgical trends, and our study was retrospective, we did not attempt to analyze our OSA population or quantify the effect of surgery. In general, both parents and patients universally were gratified with the immediate relief afforded by surgery. Excellent prospective studies of OSA and the effects of T&A can be found in the literature and will be reviewed below.

DISCUSSION

History of T&A for Infection. Tonsil surgery, although well documented by the Greeks[15] (Celsus, 50 AD), had a slow start due to a wholesome respect for postoperative hemorrhage. The guillotine tonsillotome[16] (Physick, 1827) allowed rapid extraction of the tonsils; but it was dissection tonsillectomy[17] (Crowe, 1917), combined with ether anesthesia, supine operative position, and special mouth gags, that greatly curtailed the dreaded complications of aspiration and lung abscess. Performance of the first rational adenoidectomy[18] (Meyer, 1867) and discovery of the curious ringlike arrangement of lymphoid tissue at the juncture of the food and air passages[19] (Waldeyer, 1884) provided the final ingredients necessary for the birth of the "T&A" procedure.

The surgical fervor of the times, improvements in operative technique, and the prevailing concept of focal tonsillar infection as a source of systemic disease set the stage for mass tonsillectomy. Indeed, in the preantibiotic era, T&A was practically a public health measure against deep neck abscesses, septic emboli, diphtheria, and poststreptococcal glomerulonephritis and rheumatic fever. Enthusiasm surpassed reason, however, when in the 1930s T&A for "catarrhal children" and "rheumatic symptoms" comprised one third of all surgical procedures in the United States and snatched 50% to 75% of all British children's tonsils.[1]

Flimsy indications for surgery (including "voice defects, neuralgia, iritis, debility, chorea, and dullness"[20]), unacceptably high mortality (about 1 in 2,000), and criticism from inside and outside the medical community started the decline of T&A in the 1940s.[21] Treatment of pharyngotonsillitis and otitis media with antibiotics and pressure equalization tubes resulted in a drop in yearly T&As in the United States from 1,400,000 in 1959 to 500,000 in 1979.[13] Concern over the immunologic effects of tonsillectomy[22,23] also has contributed to this decline, although there does not appear to be any increased frequency of postoperative infection when patients are compared with age-matched controls.[24]

History of T&A for Obstruction. Amid this era of surgical conservatism, Spector and Bautista[25] reported two young children with acute upper respiratory tract obstruction secondary to tonsilloadenitis, one of whom required tracheotomy. A decade later came the first descriptions of a syndrome of pulmonary hypertension, cor pulmonale, and congestive heart failure, which could be reversed by T&A or irradiation of the nasopharynx.[26,27] The following year, Gastaut et al[28] noted that similar symptoms, as well as hypersomnolence, could be caused by intermittent airway obstruction in sleeping adults, a condition subsequently termed obstructive sleep apnea.

By the mid-1970s, it became clear that OSA was an affliction not only of adults, but also of infants and children.[6,7,29] Adenotonsillar hypertrophy emerged as the principal etiologic factor, with T&A providing prompt and dramatic relief in most cases.

Sleep Apnea in Children. Obstructive sleep apnea is a functional upper airway obstruction, specifically induced by sleep,[6] with obstruction occurring whenever the collapsing force of negative inspiratory pressure exceeds the dilating force of oropharyngeal muscular contraction.[5] Afflicted children suffer from prolonged partial obstruction,[5] predominantly due to adenotonsillar hypertrophy,[3,10,30] and less often due to craniofacial dysplasia, an obstructing pharyngeal flap, or a neuromuscular disorder. Conversely, adults generally exhibit intermittent complete obstruction, without any demonstrable anatomic lesion. Obesity is a predisposing factor in all age groups.[31,32] Apneic spells are terminated by arousal from sleep stimulated by asphyxia. If apnea goes untreated, sleep fragmentation and chronic hypoxia may depress the arousal mechanism, with the potential for anoxic brain damage, pulmonary hypertension, congestive heart failure, vagal bradycardia, and sudden death.[4]

The dramatic rise in childhood OSA noted in this study and in others,[12,14] and the potential morbidity and mortality associated with delay in treatment, make early recognition and diagnosis mandatory. Although children of any age may be affected, most cases occur in young children, often less than 3 years old.[5,7,9-11] A slight male predominance has been observed by us as well as others.[5,10,12] Snoring, mouth breathing, irregular respirations, and restless sleep are nearly universal; nocturnal enuresis, poor school performance, hyperactivity, morning irritability, failure to thrive, and short stature also have been reported.[2,3,6,10,11,14,33,34] Of interest is that many of these same symptoms first appeared in the early 1900s under the heading of "reflex neuroses," a childhood disorder believed to be secondary to chronic nasal obstruction.[17]

Definitive diagnosis of OSA is made most often by polysomnography,[3] with apnea defined as a cessation of respiratory flow for at least 10 seconds in older infants and children and at least 15 seconds in infants of less than 52 weeks' postconceptional age.[5] If polysomnography is not available, the most reliable clinical symptom is loud snoring, occurring all night and every night, interrupted by periods of silence (apnea) that are terminated by snorting sounds and agitated arousal indicating resumption of airflow.[3,5,11] Apneic events per se, however, seldom are related by parents.[10] Hypersomnolence and obesity occur much less frequently in children than in adults.

Role of T&A in Sleep Apnea. Children with OSA commonly have large tonsils with a common medial contact point.[12] Mirror or fiberoptic examination of the lower tonsillar pole is essential, since the airway narrows toward the hypopharynx, and isolated caudad hypertrophy can occur.[14] Even in the absence of clinical tonsillar hypertrophy, tonsillectomy has relieved OSA in children.[10,11] The palatoglossal fold may obscure a significant portion of the tonsil,[35] and in the supine position, in which the tongue and soft tissues of the oropharynx fall backward, even small tonsils can cause obstruction. Likewise, even mild to moderate adenoid hypertrophy may be associated with significant OSA. In children with minimal or no adenotonsillar hypertrophy, sleep videofluoroscopy often demonstrates that the tonsils and adenoids nonetheless play a major role in the airway obstruction, especially if associated with craniofacial dysplasia or neurologic disorders.[36]

The efficacy of tonsillectomy, with or without adenoidectomy, in the relief of OSA in children[3,5-7,9-11,31] and adults[30,37,38] is well established. Reduction in the number of obstructive apneas has been shown to reduce the number of central apneas.[8] Children with Down syndrome are predisposed to OSA because of increased tongue volume and generalized hypotonia. In these patients, T&A is effective, but an adjunctive pharyngoplasty may be required, and the risk of postadenoidectomy velopharyngeal insufficiency is increased.[39,40] Tracheotomy rarely is required for OSA in children.

Recent studies show that T&A is also highly effective in children who do not have true OSA but suffer from less severe symptoms including loud snoring (without apnea), night cough, mouth breathing, breath-holding, hypersomnolence, and abnormal daytime behavior.[41-43] Adenotonsillar hypertrophy is apparently capable of causing a spectrum of obstructive symptoms, ranging from isolated snoring to OSA, congestive heart failure, and sudden death, respectively. At the present time it is unclear why certain children are more susceptible to the effects of adenotonsillar hypertrophy than others. The use of T&A for obstructive symptoms without OSA must take into consideration the morbidity associated with a 2% to 5% incidence of postoperative bleeding,[44] and the present mortality estimates that range from 1:16,000[45] to 1:150,000.[24]

Changing Indications for T&A. After nearly 2,000 years of experience with tonsillectomy for inflammation, obstruction has emerged as an increasingly important reason for surgery. The efficacy of tonsillectomy for severe recurrent pharyngitis[46] and OSA has been proven recently, but the role of the procedure for less severe inflammatory and obstructive conditions remains controversial. Even peritonsillar abscess is no longer an absolute indication for surgery.[47] Indications for adenoidectomy likewise have become more conservative, but the adenoids do appear to play a role in both unremitting otitis media[48,49] and OSA.

We presently consider tonsillectomy the procedure of choice for patients with OSA and tonsillar hypertrophy. Adenoidectomy is performed concurrently in those patients with adenoidal hypertrophy and clinical nasopharyngeal obstruction. Adenoidectomy alone is indicated in the less common situation of OSA in a patient with obstructive adenoids but normal tonsils. Corrective nasal surgery (turbinectomy, septoplasty) is employed as needed.

CONCLUSIONS

The trend toward fewer tonsil and adenoid procedures begun in the 1930s still continues. Infection remains the predominant indication for surgery, but tonsillectomy, with or without adenoidectomy, is assuming an increasingly important role in the management of OSA.

A dramatic increase has occurred in the percentage of T&As performed for OSA due to adenotonsillar hypertrophy. Whether this is due to an increase in OSA incidence, an increase in diagnosis, or an increase in the number of children with adenotonsillar hypertrophy is uncertain.

In children, OSA has diverse manifestations, with loud continuous snoring reported as the most nearly universal symptom. Early diagnosis of OSA and timely performance of T&A may prevent serious cardiovascular, pulmonary, and neurologic complications. Greater awareness of OSA in the general pediatric population and an appreciation of the differences between OSA in children and that in adults is required.

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EXPERIENCE OF A PERMANENT VENTILATION AND DRAINAGE SYSTEM IN THE MANAGEMENT OF PURULENT MAXILLARY SINUSITIS

OLOF BERG, MD, PHD LARS LEJDEBORN, MD

STOCKHOLM, SWEDEN

Fifty patients with purulent maxillary sinusitis, 11 patients with pressure-induced maxillary pain, and 14 patients undergoing maxillary sinus surgery were treated with a new type of permanent ventilation and drainage tube. With use of local anesthesia and as an office procedure, an inferior meatus antrostomy was performed with a circular-bore trephine, and a medical-grade, x-ray-dense silicone tube was inserted to secure the ventilation and drainage. Experience of 14 months of clinical use demonstrated a high success rate (92%) in cases of recurrent and chronic purulent sinusitis. All patients with pressure-induced pain were free from symptoms throughout the observation time. Only a few minor complications were observed. Among the advantages of the method is a more aggressive and early treatment in cases of purulent maxillary infections, possibly prior to the development of irreversible mucosal damage.

KEY WORDS — maxillary sinusitis, permanent ventilation and drainage, prophylaxis.

INTRODUCTION

Recent studies on the pathophysiology of purulent maxillary sinusitis have emphasized the importance of repeated drainage as a major therapeutic principle. The purulent maxillary secretion, characterized by low pH and P_{O2} but high levels of P_{CO2}[1] and low levels of immunoglobulins[2] and high proteolytic activity,[3] offers a poor environment for host-defense mechanisms. Repeated drainage increases the local content of immunoglobulins[2] and reduces the proteolytic activity.[4]

The diagnosis of purulent maxillary sinusitis is suspected after a thorough clinical examination[5] and confirmed by an antral aspiration.[6] This procedure has a high sensitivity (85%), and unnecessary antral punctures are performed in less than 20% of cases. With or without antimicrobial therapy, many patients will need no further drainage in order to heal.[7] Therapeutic failures are, however, frequent occurrences, and if these conditions are not recognized and treated efficiently, the infection might take a prolonged or chronic course. The choice of therapy in these cases is merely a question of how radical the drainage has to be. Repeated irrigations have the disadvantage of perhaps presenting discomfort to the patient, as well as being time- and resource-consuming for the health-care sector. Furthermore, the drainage and ventilation are not supported between each irrigation. Accordingly, many attempts have been made to introduce different kind of tubes into the maxillary sinus in order to provide a more permanent drainage of and access to the sinus cavity.[8-12] So far none of these methods seems to have gained the wide acceptance that the procedure deserves. One reason could be that the tube is introduced by a rather large trocar,[9-11] which makes the insertion of the tube as uncomfortable as a regular endonasal trephination. When the tube is introduced through an ordinary cannula,[12] the inner diameter of the tube, for obvious reasons, cannot be very wide. Furthermore, these tubes are designed either to hang out of the nose or to reach the vestibulum with their outer end, which does not facilitate the use of the tubes for more than a limited period of time. This design does not allow the tubes to be used as a continuous prophylaxis in cases of recurrent purulent sinusitis or pressure change–induced sinus pain.

From both a theoretic and practical point of view, it seems desirable to use a short drainage and ventilation tube with a sufficiently large inner diameter to allow free disposal of secretion into the nasal cavity as well as air to the antrum. The design of the tube should avoid accidental loss into the sinus or the nasal cavity. The tube should be manufactured in a biocompatible x-ray–dense material that allows the tube to remain in position as long as desired. The insertion of the tube should be relatively simple, preferably performed as an office procedure after diagnostic antral aspiration and, when considered necessary, sinoscopy. During treatment and prophylaxis, inspection and irrigation of and suction through the drainage tube should be possible.

MATERIAL AND METHODS

Patients. In all, 77 patients (51 women and 26 men; mean age, 43.1 years) were studied. Twenty-four patients suffered from recurrent purulent maxillary sinusitis, defined as three or more (aspiration-verified) purulent infections during the preceding

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year. Twenty-six patients had a chronic purulent sinusitis with a history of over 3 months and they all had been subjected to antibiotic treatment and, in 17 cases, repeated irrigations. Another 14 patients had received a drainage tube in connection with maxillary sinus surgery for reasons other than infections, instead of having had a broad endonasal communication in the Caldwell-Luc procedure. Eleven patients had severe problems with equalizing pressure in the maxillary sinuses during pressure changes. Nine of these patients were members of an aircrew and two were professional scuba divers. Another two patients experienced diffuse pain in the maxillary sinus region. Antral aspiration and sinoscopy showed normal conditions, as did conventional radiography and computed tomography. Neither the consultant dentist nor neurologist could demonstrate any disease within the area or give a plausible explanation for the conditions. In these two cases the drainage tube was introduced to exclude an unrecognized ostial dysfunction.

Among the 50 patients with either recurrent or chronic purulent sinusitis, antral aspiration was performed under local anesthesia (naphazoline/lidocaine and Xylocaine spray 40 mg/mL; Astra) in all cases, in order to establish the purulent character of the retained secretion. In the other 27 cases, no antral aspiration prior to the introduction of the drainage tube was performed.

Instrument Description. The instrument consists of a circular-bore trephine with a diameter of 5 mm, manufactured either in stainless steel for resterilization or in a disposable plastic material (ATOS SinoVent, ATOS Medical, Hörby, Sweden). The drainage and ventilation tube is manufactured in medical-grade, x-ray–dense silicone, and a guide pin and pusher are used to install the tube (see Figure, A). After the patient is given a decongestant and local anesthetic, the trephine is introduced under the inferior concha, and by easy pressure and rotation back and forth, an almost circular hole is obtained into the maxillary sinus (see Figure, B). The bone plug will remain in the bore, and no tissue will be deposited within the sinus cavity when the trephine is removed. A straight guide pin then is introduced through the hole, and the drainage and ventilation tube is slid and, when in the nasal cavity, is pushed (see Figure, C) by the pusher into the proper position (see Figure, D). The outer, large flange prevents the tube from being lost in the antrum, and the inner, soft flange secures the tube from escaping into the nasal cavity. When desired, suction and irrigation is possible with standard equipment, preferably after administration of a local vasoconstrictor, since the tube is often partly hidden under the inferior concha. Removal of the tube offers no problems, since the inner flange does not resist other than minor extraction forces.

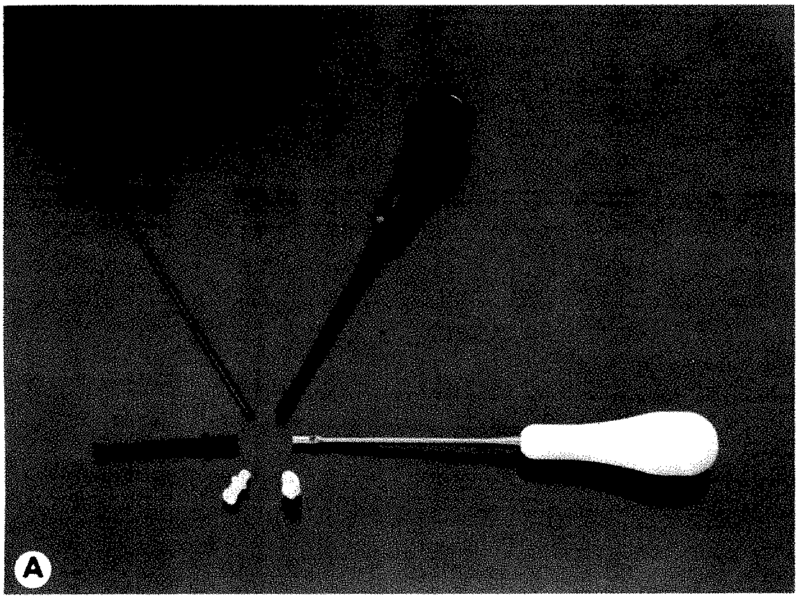
Technique. With use of local anesthesia as described above, or in five cases general anesthesia, the trephine was positioned under the inferior concha, in many cases after luxation of the concha, somewhat more ventral in the nasal cavity than would be customary in regular sinus puncture. By use of this technique the insertion of and future inspection of the tube were facilitated. With a slight pressure and by rotating the trephine, we achieved a hole into the sinus cavity. In most cases, sinoscopy through the hole also was performed to confirm the preliminary diagnosis. The guide was introduced and brought into contact with the back wall of the sinus cavity and the drainage tube was pushed by the pusher to a proper position. By use of pressure firm enough to push the inner flange through the hole into the antrum, but not so firm as to push the outer collar from the nasal cavity, the tube was positioned accurately. The guide and pusher then were removed. To ensure a stable position, a gentle attempt was made with forceps to pull the drain tube out. If any bleeding occurred, a piece of gauze was left in the nasal cavity for some hours. The patients were seen at the office after 1 week and thereafter every 2 or 3 months.

RESULTS

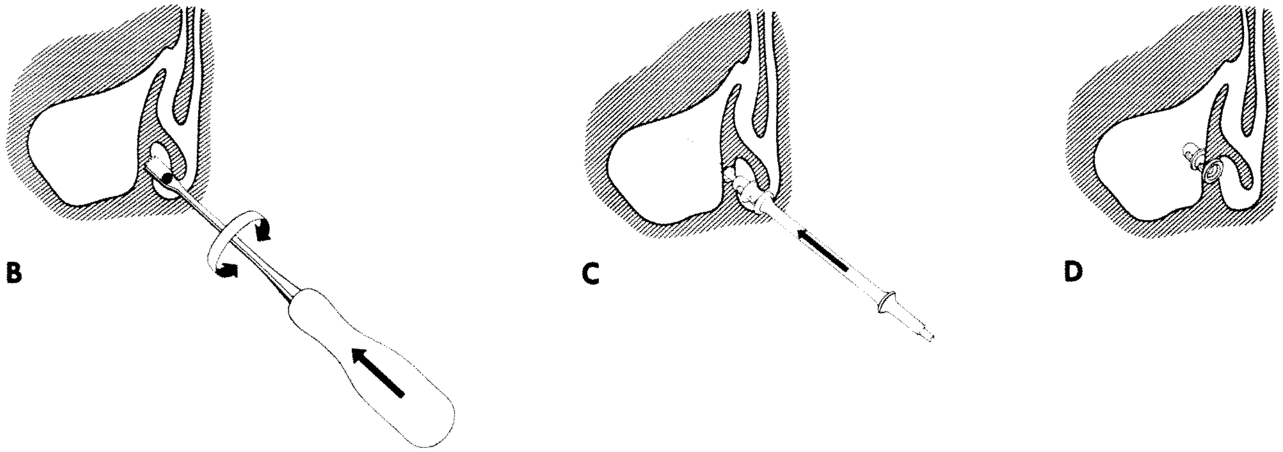
Seventy-seven patients received a total of 112 drain tubes over a period of 14 months (May 1987 to July 1988), with an elapsed observation time of 466 months. Three drain tubes fell out into the nasal cavity: in one case the patient sneezed the tube out, and in the other case, two loose tubes were removed at the first follow-up office visit. These two patients were numbers 4 and 7 in the series.

Two drain tubes were lost into the maxillary sinus. In one case of chronic maxillary sinusitis, an antrostomy had been performed some years previously but had been reorganized. The medial wall of the antrum thus was less well defined, and the tube was pushed into the cavity during insertion. By means of sinoscopy, the tube was located and removed. In another case of chronic purulent sinusitis, the drain tube was retrieved from the antrum during a Caldwell-Luc procedure that was performed because of failure of the sinus to be cured with the drain tube. Whether the tube was in the sinus cavity prior to the operation or was forced in during the insertion could not be established.

Among 24 patients with recurrent purulent sinusitis, 21 had no complaints after installation of the tubes in their maxillary sinuses during the observation period (elapsed time, 185 months), nor did they demonstrate any evidence of sinusitis or other sinus disorder on follow-up. Two patients still experienced discomfort, but the examinations revealed no evidence of purulent sinusitis, and aspirations through the drain tubes were free of purulent secretions. Neither of these two patients required further surgical therapy. One patient did not heal



Instrument and technique used. A) Bore, either disposable or stainless steel, ventilation and drainage tube, and guide pin and pusher for insertion of tube. B) Bore is introduced under inferior concha, and by easy pressure and rotation back and forth, almost circular hole into maxillary sinus is obtained. C) Guide pin is introduced through hole into sinus cavity. Tube is slid and pushed into proper position. D) Ventilation and drainage tube in secure position, ensuring permanent antronasal communication.



with use of the drain tube, and surgery with gingival flap antrotomy[13] was performed 5 months after the insertion of the tube.

Among 26 patients with chronic purulent maxillary sinusitis receiving the drain and ventilation tube, 24 were free from symptoms during the follow-up (mean, 7.2 months). Clinical controls, including aspiration through the tube, did not demonstrate any purulent secretion in the affected sinus. Two patients did not heal and required antrotomy within 2 months.

In 14 cases, the tube was inserted for postoperative drainage and ventilation following antrotomy with removal of large symptomatous intramural maxillary cysts.[14,15] The tubes were removed 2 or 3 weeks postoperatively. No complications in the healing process were observed among this group of patients.

The ventilation tube treatment was successful in all 11 patients with pressure-induced maxillary pain during airplane flights or diving, and the patients were free from symptoms during the observation period (mean, 8.3 months). Two patients were treated with ventilation tubes for differential diagnostic purposes in order to exclude any unrecognized maxillary ostium dysfunction. One of the patients improved and no further therapy was necessary. The other case was less successful: the tubes were removed after 3 weeks, and the patient was cared for by a neurologist.

Because of some bleeding during insertion of the tubes, it was necessary in eight cases to place gauze in the nasal cavity postoperatively. The gauze was removed by the patients some hours later. No case of postoperative bleeding that would demand treatment was registered among the 77 patients.

Three cases of postoperative infections were registered. One patient presented a swollen cheek and a mild fever 3 days postoperatively. This complication was probably due to the fact that the hole was positioned too far ventral in the nasal cavity and affected the anterior wall of the maxillary sinus. The infection healed promptly with antibiotic therapy, and the tube was not removed. The following course was satisfactory, and the patient's drainage and ventilation tube remains in position. Two patients experienced crust formation in the nasal cavity around the tubes. Bacteriologic culture demonstrated growth of *Staphylococcus aureus*, but the patients' general condition was never affected. In both cases, the infections healed completely with local therapy, and the tubes were not removed. Hyperesthesia in one or two teeth was noted in three cases, but the sensibility of the teeth was normal within 3 months.

DISCUSSION

The beneficial effects of drainage in cases of purulent maxillary sinusitis are well documented. The restoration of ventilation as a major factor in the healing process also has been demonstrated in recent publications.[16-19] After antrostomy, even severe mucosal disease, in the past considered to be irreversible, is reported to undergo resolution with restoration of the mucociliary clearance toward the natural ostium. From at least a theoretic point of view the treatment of purulent sinusitis should be aggressive and without delay. Adequate drainage and ventilation should be secured early in the disease to avoid the harmful effects of long-standing high proteolytic activity on the mucosa. Furthermore, the obvious risk of recurrent infections should be considered.

Until recently, inferior antrostomy has been the standard procedure for achieving drainage and ventilation of the maxillary sinus. Successful cases are being reported at a rate well over 90%,[20] but a large opening (more than 1 x 1 cm) is required to secure a permanent antrostomy.[19] As a result of the rapid development of nasal endoscopy, endoscopic surgery on the osteomeatal complex[21-24] offers a new technique for obtaining sufficient ventilation and drainage. After removal of the uncinate process, and often the ethmoid bulla, a narrow maxillary ostium can be widened. If necessary, diseased ethmoid cells can be opened and cleared. This method certainly seems to offer considerable advantages in cases in which the ethmoid sinuses and the osteomeatal complex are thought to be the primary focus of disease. In many cases, however, disease in the middle meatus could be regarded as secondary to a purulent flow from the infected maxillary sinus, and subsequently no beneficial effects of surgery on the osteomeatal complex can be expected.[25,26] Furthermore, functional endoscopic surgery should be confined to specially trained otorhinolaryngologists, since there is an increased risk of complications during the procedure compared to a regular antrostomy. If osteomeatal surgery is performed on selected cases and regarded as "step 2" when the inferior antrostomy fails, an optimum balance between the procedures is achieved and thus a maximum number of patients are cured with a minimum of hazard.

It seems that our new technique for obtaining an inferior antrostomy offers a solution to an old dilemma. With the circular trephine, an exactly defined opening into the antrum is obtained, which is necessary if a tube is to be inserted and securely positioned. Since the procedure is not more extensive than a regular sinus puncture, it is possible to perform in an office setting with the patient sitting up. The ventilation and drainage tube, manufactured in medical-grade silicone, avoids the risk of occlusion of the antrostomy, which frequently occurs with the conventional technique. The small size of the tube and the position in the inferior meatus explain why none of our 77 patients revealed any discomfort or increased nasal discharge once the purulent sinusitis was healed.

A comparison between the results in this study and previous reports is difficult to make. Strict definitions of duration, character of the secretion, and host-defense reaction, and histopathologic examination of mucosal specimens prior to and after treatment would be necessary. However, among our 50 patients who had either recurrent or chronic purulent sinusitis, 46 (92%) were cured and required no further therapy during the observation time. This result is close to what previously has been reported when a large antrostomy is performed.[19,20] Whether these promising results are maintained over an extended period of time has yet to be evaluated.

In our experience, complications during the insertion of the ventilation and drainage tube were rare. Bleeding and infection seldom occurred, and once the technique was refined, no tubes were lost in the nasal cavity accidentally. The risk of forcing the tube into the antrum was minimized when only patients with an intact medial wall were considered as candidates for this therapy. A temporary hyperesthesia of one or two frontal teeth was observed in three cases. Whether this was due to an actual trauma to accessory nerves, or just reflex ischemia and disturbed microcirculation of the nerves in the area caused by the use of local vasoconstrictors in connection with insertion of the tubes, could not be determined.

The possibility of treating purulent maxillary sinusitis by relatively simple means and as an office procedure, aggressively, at an early stage of morbidity, and prior to the development of perhaps irreversible mucosal damage offers an interesting new line of therapy. Promising results in the treatment of pressure-induced pain, as well as an easily installed and removed postoperative drainage, contribute to the advantages of the method. Further studies will be performed.

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DIZZINESS MANAGEMENT CONFERENCE

The Department of Otolaryngology and Audiology Services, Medical College of Ohio, will host a Dizziness Management Conference on June 9, 1990. For further information, contact Randa Mansour-Shousher, MS, CCC-A, Audiology, Medical College of Ohio, 3000 Arlington Avenue, Toledo, OH 43614; (419) 381-4012.

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SURGEONS' REPORTED ATTITUDES AND PRACTICES REGARDING ALARYNGEAL SPEECH

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Attitudes and practices of 50 prominent laryngologic surgeons were surveyed to determine current trends and implications for postoperative speech rehabilitation. Data are available for 1,003 laryngectomy operations performed over the past 3-year period by the 22 responders (44%). Those surgeons responding indicated a preference toward tracheoesophageal shunt procedures. A negative correlation was noted between the increased number of tracheoesophageal shunt procedures and the age of the surgeon. Additional responses provided information regarding personal preferences for postlaryngectomy speech types, opinions regarding artificial device use, and speech rehabilitation referral practices.

KEY WORDS — alaryngeal speech, laryngectomy.

Rehabilitation of the laryngectomy candidate must begin as soon as the diagnosis of laryngeal cancer is made. This requires that the surgeon have a philosophy regarding issues such as preoperative counseling, procedures for referral, methods of postoperative communication, and termination of therapy services, since the surgeon's responsibility is the patient's total rehabilitation. He or she functions as the primary coordinator of rehabilitation.

Attitudes toward preoperative counseling involve several issues, among which are 1) How much should the patient be told? and 2) Who should provide the counseling? Johnson et al,[1] in their survey of postlaryngectomy patients, found that almost all of them felt inadequately prepared by the surgeon's preoperative counseling. Following this survey, the authors sent questionnaires to 1,276 otolaryngologists practicing in the northeastern United States. Two thirds of the responders believed their patients should be fully informed preoperatively of the disease and its treatment. They further reported that the younger surgeons surveyed generally used a "rehabilitative team" approach, while older surgeons most often did their own counseling, sometimes with assistance from a successfully rehabilitated laryngectomee. Salmon[2] reported that only 56% of the patients she surveyed believed that they were informed adequately before the operation. Bralley et al,[3] in a study of laryngectomy candidates and their spouses, found that 33% of the couples were not informed of the diagnosis together, but that one member of the couple had the difficult, and most likely unwanted, task of telling the other. Kommers et al[4] reported that counseling needs may vary according to the patient's age. They found that older patients and their spouses focus on the possibility of death, while younger patients and their spouses may not fully understand the prospective changes in lifestyle. They believe that a "team" should be involved from the onset to prevent feelings of isolation and despair. Duguay[5] found that the preoperative perceptions of laryngectomy candidates regarding postoperative speech management are "generally unrealistic and often are completely contrary to fact."

Although it is questionable as to how much information is retained when the candidate is dealing concurrently with the psychological trauma of having cancer, individualized counseling with the provision of as much information as possible from a variety of sources (ie, surgeon, speech pathologist, American Cancer Society, laryngectomized individual) generally appears to be in the best interest of the patient and family. Preoperative counseling should afford the patient a greater opportunity to consider the number of different issues that confront him or her regarding the surgery and its consequences. In addition, the issues of quality versus quantity of life should not be overlooked.[6]

Postoperative communication options are another major consideration in laryngectomy rehabilitation. Lauder's[7] initial look at the attitudes toward the artificial larynx found a division of opinions in the physicians, speech pathologists, and laryngectomees polled. Opponents to the use of an artificial larynx felt that these devices had too many limitations and would interfere with the development of intelligible esophageal speech. Advocates indicated that devices provide a positive psychological impetus that should not interfere with the acquisition of esophageal speech as long as proper training is provided. In a later article, Lauder[8] proposed that the artificial larynx should be an option for the laryngectomee while or instead of learning esophageal speech, and for use in emergency situa-

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RESULTS OF SURVEY

Number of reported laryngectomies performed in past 3 years by 22 responders	*1,003*
Percentage of patients using particular type of alaryngeal speech to communicate postoperatively	
Surgical prosthetic speech (tracheoesophageal shunt)	*38.10%*
Artificial device speech	*21.77%*
Esophageal speech	*21.50%*
Esophageal speech and artificial device speech	*17.18%*
Surgically restored speech (Asai, etc)	*0%*
Unknown	*1.45%*
Person(s) deciding method(s) of speech used	
Combination of surgeon, patient, and speech pathologist	*45.45%*
Surgeon and patient	*18.18%*
Surgeon	*13.64%*
Surgeon and speech pathologist	*9.08%*
Patient and speech pathologist	*4.55%*
Patient	*4.55%*
Speech pathologist	*4.55%*
Percentage of surgeons who report discussing postoperative speech options with patient	*95%*
Speech options that reportedly were presented by surgeons to their patients	
Esophageal; tracheoesopheal shunt; artificial device	*86.35%*
Esophageal; tracheoesophageal shunt	*4.55%*
Esophageal only	*4.55%*
Tracheoesophageal shunt only	*0%*
Artificial device only	*0%*
Percentage of surgeons who reportedly refer for speech rehabilitation	*100%*
Surgeons refer to	
Speech pathologist	*50%*
Speech pathologist and laryngectomee	*45.45%*
Unknown	*4.50%*
Percentage of surgeons referring	
Preoperatively; postoperatively (inpatient); postoperatively (outpatient)	*40.91%*
Preoperatively only	*31.81%*
Preoperatively and postoperatively (inpatient)	*13.63%*
Postoperatively (inpatient); postoperatively (outpatient)	*4.55%*
Postoperatively (inpatient) only	*4.55%*
Postoperatively (outpatient) only	*4.55%*
Percentage of surgeons permitting use of artificial device	
Whenever recommended by speech pathologist	*86.30%*
Before attempting esophageal speech	*9.09%*
Upon failure to develop esophageal speech	*4.55%*
Percentage of surgeons who refuse to allow patient to use device	*0%*
Decision to terminate speech therapy is made by	
Speech pathologist	*36.36%*
Surgeon and speech pathologist	*18.18%*
Speech pathologist and patient	*18.18%*
Surgeon, speech pathologist, and patient	*13.63%*
Surgeon and patient	*4.55%*
Patient	*4.55%*
Unknown	*4.55%*
Surgeon	*0%*
Surgeon's expressed preference of speech modality	
Esophageal speech	*45.45%*
Tracheoesophageal shunt speech	*36.36%*
No preference	*13.64%*
Esophageal speech and artificial device speech	*4.55%*
Surgeon's age	
61-70	*31.82%*
51-60	*22.72%*
41-45	*18.18%*
46-50	*9.09%*
36-40	*9.09%*
30-35	*4.55%*
70+	*4.55%*
Mean percentage of tracheoesophageal shunt procedures relative to laryngectomy caseload, by surgeon's age	
30-35	*80.00%*
36-40	*55.00%*
41-45	*48.75%*
46-50	*42.00%*
51-60	*40.40%*
61-70	*22.43%*
70+	*10.00%*

tions. Gates et al[9] proposed that postlaryngectomy voicelessness is a cause of psychological trauma in the patient, and found[10] that use of the electrolarynx did not correlate with failure to develop esophageal speech. Duguay[11] and Goode[12] encourage early, unprejudiced exposure to the artificial larynx to prevent any negative attitudes toward a device and to provide a means of postoperative communication. Edelman[13] questioned whether laryngectomees were being limited by the prejudices of some rehabilitators by the establishment of a hierarchy of postoperative speech forms. In her survey of the attitudes and practices of speech pathologists, Edelman found that they generally provide an artificial device in conjunction with esophageal voice instruction, thus enhancing acceptance of the device rather than forming an "if you can't...then..." dichotomy. She found that the otolaryngologists surveyed preferred withholding recommendations for devices until esophageal speech therapy had been attempted.

In studies of alaryngeal speech intelligibility, Clark[14] found that in the presence of auditory competition (speech) the artificial device offered the highest degree and tracheoesophageal speech the lowest degree of intelligibility for older listeners. This is important when one considers that the mean age of laryngectomees at the time of surgery is 55 years of age.[15] It is reasonable to suggest that a significant number of friends and family members of the laryngectomee are also within that age range, an age noteworthy for the presence of presbycusis. Ryan et al[16] suggested that even under ideal conditions the low pitch and volume of esophageal speech create problems for the listener. McCrosky and Mulligan[17] found that intelligibility of esophageal speech and artificial device speech was influenced by the professional training of the listener. Speech clinicians rated esophageal speech as being more intelligible, while naive listeners gave higher intelligibility ratings to artificial device speech. There are obviously a number of effective ways to communicate orally after laryngectomy, and some ways will be more appropriate than others for a given patient.

The past few years have witnessed a number of surgical and surgical-prosthetic approaches to voice restoration after laryngectomy. Lopez et al,[18] in a random sample of 1,999 head and neck surgeons selected from the directory of the American Academy of Otolaryngology, found that 88% of them use tracheoesophageal puncture as a type of speech restoration procedure.

In contrast to the Lopez et al study, it is the intent of these authors to report the current practices of a select group of laryngologic surgeons recognized as being outstanding in their field by 10 of the nation's most active speech pathologists in the area of alaryngeal speech. In addition to voice restoration approaches, the surgeons' viewpoints on counseling, utilization of speech clinicians, artificial devices, and postoperative speech methods will be addressed.

METHODS

Ten speech-language pathologists nationally known for their experience in clinical work and published research in alaryngeal speech rehabilitation were asked to identify the five most prominent laryngologic surgeons in their region of the country. Questionnaires were forwarded to these 50 surgeons asking about their current clinical practices in an attempt to determine their attitudes regarding various aspects of postlaryngectomy speech rehabilitation. Twenty-two surgeons returned the questionnaires, representing a return rate of 44%. These responses included surgeons practicing in the states of California, Colorado, Connecticut, Florida, Illinois, Kansas, Massachusetts, Michigan, New York, and Texas.

The 22 responding surgeons reported information for a total number of 1,003 laryngectomy operations performed over the past 3-year period. Percentages were computed for the 1,003 patients regarding use of esophageal speech, artificial devices, a combination of esophageal speech and artificial devices, surgically restored speech (Asai, etc), and surgical prosthetic speech (tracheoesophageal shunt). In addition, the surgeons surveyed were asked about their attitudes toward the use of artificial devices, sources for and timing of referrals, their personal preferences for postlaryngectomy speech methods, and termination of speech therapy services.

RESULTS AND COMMENTS

The findings are summarized in the Table.

The intent of this study was to determine the practices and trends being established by the leading laryngologic surgeons in the United States. In analyzing the data, five major trends were noted.

1. The most prevalent type of postlaryngectomy speech used was tracheoesophageal shunt speech (38.10%).
2. All surgeons referred for speech rehabilitation.
3. All surgeons allowed the use of an artificial device.
4. Surgeons' preferences for postlaryngectomy speech were esophageal (45.45%) and tracheoesophageal shunt speech (36.36%).
5. There was a negative correlation between the age of the surgeon and the number of tracheoesophageal shunt procedures performed.

Because of the small sample of surgeons (n = 22), the authors are sensitive to the issue of generalization. However, the surgeons surveyed were identified as leading practitioners in their field, and the data obtained are regarded as indicative of current high quality practices. In addition, since the surgeons who returned the questionnaires were not asked to identify themselves, one can only assume that the data are reliable and/or that the sample size (n = 1,003) is sufficient to control for bias.

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY
THE MESSERKLINGER TECHNIQUE

A course entitled Functional Endoscopic Sinus Surgery — The Messerklinger Technique will be held July 5-7, 1990, in Graz, Austria. For further information, contact Prof H. Stammberger, MD, University ENT-Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria.

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THIRD INTERNATIONAL SYMPOSIUM AND WORKSHOPS ON SURGERY OF THE INNER EAR

The Third International Symposium and Workshops on Surgery of the Inner Ear will be held July 29-August 4, 1990, in Snowmass-Aspen, Colorado. For further information, contact Maurine Taylor, c/o I. Kaufman Arenberg, MD, 300 East Hampden Avenue, Suite 401, Englewood, CO 80110.

Ann Otol Rhinol Laryngol 99:1990

DAILY FLUCTUATIONS OF MIDDLE EAR PRESSURE IN ATELECTATIC EARS

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The position of the drum of 84 atelectatic ears, of patients 5 to 79 years old, was examined with the help of the operating microscope at different times of the day. All ears were found to be atelectatic during the daytime, yet on the patients' awakening in the morning, 37.73% of the drums of the adolescents' and adults' ears were found to be inflated, usually even hyperinflated. None of the children showed an inflated eardrum in the morning. All eardrums that were inflated in the morning returned to their original atelectatic position within an average of 54.56 minutes after awakening. This observation illustrates another fluctuating aspect of the atelectatic condition.

KEY WORDS — atelectasis, middle ear gases, middle ear pressure.

INTRODUCTION

It commonly is accepted that oxygen is continually absorbed from the middle ear into the circulation. The gas deficit is compensated for by reentry of air into the middle ear through the eustachian tube on swallowing. It also is accepted that the frequency of swallowing diminishes during sleep,[1] leading to the logical assumption that middle ear pressure is lower at night than during waking hours. This hypothesis is supported by reports of decreased eustachian tube function in recumbent individuals,[2] but was challenged by three recent studies. Bylander et al[1] found that middle ear tympanometric pressure in eight ears of children with "known muscular opening hypofunction" was higher during night sleep than when the subjects were awake. Hergils and Magnuson[3] also found positive tympanometric pressure in 50 ears of normal adults on awakening in the morning; this pressure returned to a lower baseline after chewing and swallowing. We found that ten of 27 atelectatic drums of adults were inflated immediately on awakening after a night's sleep.[4] All of these findings point to the development of positive pressure during sleep.

The aim of this prospective study was to examine a larger group of atelectatic ears and to extend the age range of the examined patients by including children in our study group. We also wanted to study the possible influence of middle ear effusion on nocturnal inflation of atelectatic eardrums.

MATERIAL AND METHODS

The study consisted of 58 volunteers (84 atelectatic middle ears), who were divided into three age groups: children 5 to 10 years old, adolescents 11 to 15 years old, and adults. The degree of atelectasis ranged from grade 1 to grade 3 according to the classification of Sadé et al.[5] Ears with grade 4 atelectasis, ie, the adhesive type, were excluded. The composition of the three age groups, the degree of atelectasis, and the incidence of middle ear effusion are recorded in Table 1.

All ears were examined before the patients went to sleep and immediately on awakening. The time from awakening until examination was less than a minute, during which time the patients were instructed not to sniff or swallow. Examinations were performed by three physicians using the operating microscope.

Fourteen of the 20 ears found to have inflated eardrums at the early morning examination were reexamined immediately every 2 to 10 minutes until the eardrum returned to its original atelectatic position. The results were analyzed statistically by means of the χ^2 test.

TABLE 1. DEGREE OF ATELECTASIS AND PRESENCE OF MIDDLE EAR EFFUSION IN DIFFERENT AGE GROUPS

			Atelectasis Grade 1		*Atelectasis Grade 2*		*Atelectasis Grade 3*		*Presence of Middle Ear Effusion*	
Age Group (yr)	*No. of Patients*	*No. of Atelectatic Ears**	*No. of Ears*	*%*	*No. of Ears*	*%*	*No. of Ears*	*%*	*No. of Ears*	*%*
5-10	20	31 (11)	5	16.12	12	38.70	14	45.16	27	87.09
11-15	10	13 (3)	5	38.46	4	30.76	4	30.76	8	61.53
17-79	28	40 (12)	6	15.00	15	37.50	19	47.50	19	47.50

*Number in parenthesis indicates number of patients with bilateral atelectasis.

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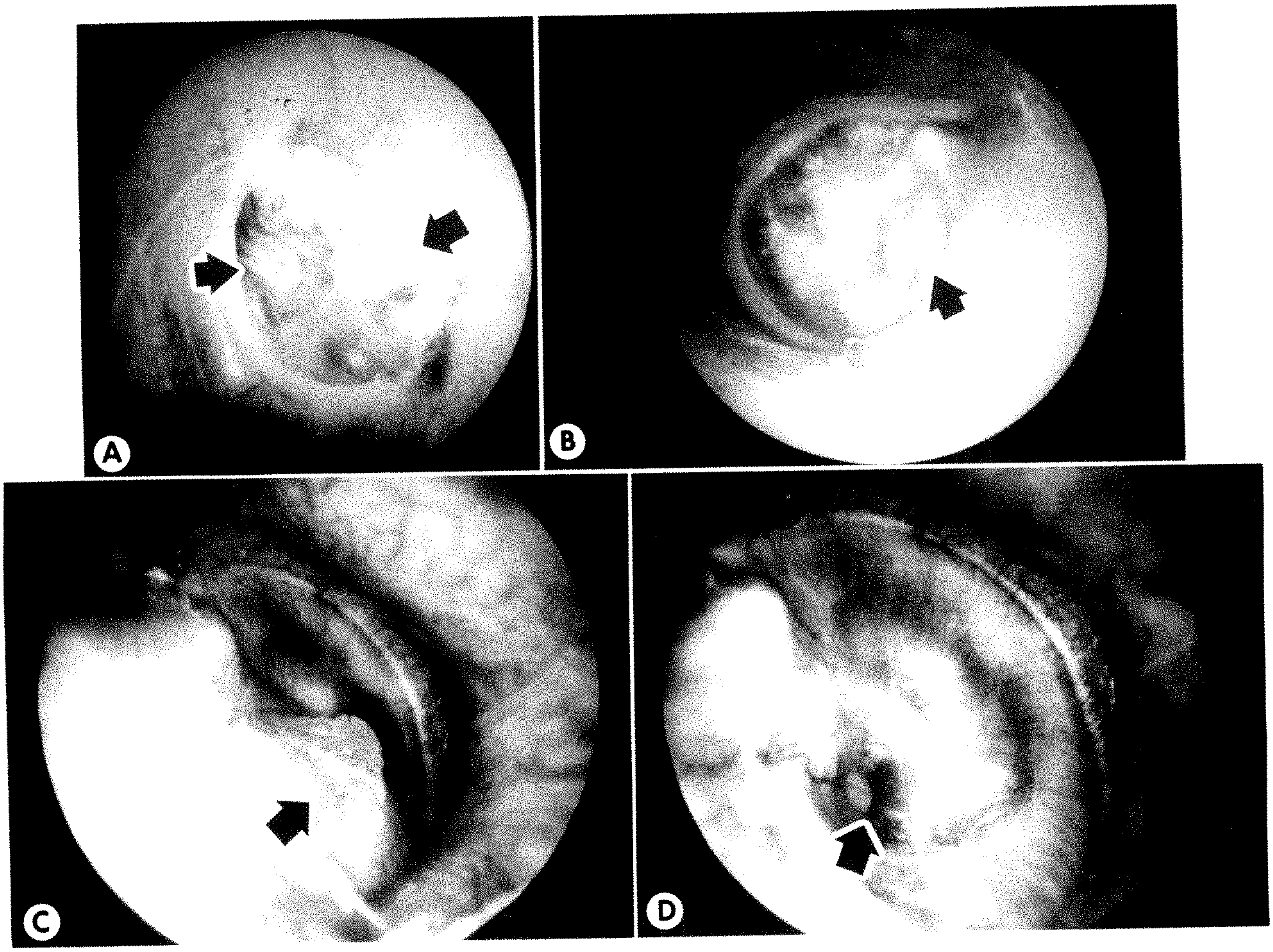

Otoscopic views of two ears with atelectasis. A) Marked ballooning of atelectatic eardrum. Arrows — anterior and posterior ballooning. B) Same ear as in A in its atelectatic position. Arrow — eardrum lying on incus. C) Another ear with ballooning of atelectatic eardrum. Arrow — posterior ballooning. D) Same ear as in C in its atelectatic position. Arrow — posterior atelectatic part of eardrum.

RESULTS

In 20 of the 84 atelectatic ears examined, the atelectasis disappeared on awakening; in fact the atelectatic parts of the eardrums usually were found to be hyperinflated, similar to those observed after politzerization (see Figure).

Table 2 records the incidence of drum inflation found at the early morning examination. None of the eardrums in the children's group (5 to 10 years of age) manifested morning inflation, but 46.15% of the adolescents (11 to 15 years of age) and 35% of the adults (17 to 79 years of age) showed a complete disappearance of their atelectasis. Of the 12 adults with bilateral atelectasis, four exhibited early morning disappearance of atelectasis in one ear only, and one showed it in both ears.

All of the 20 ears that showed a spontaneous disappearance of their atelectasis in the morning gradually reverted to their former atelectatic state. The time it took for these eardrums to return to their original atelectatic condition was measured in 14 of them and was found to range from 20 to 157.5 minutes (mean, 54.46 minutes).

Since none of the children exhibited morning autoinflation, we redivided the patients into two groups: 5 to 10 years of age and 11 to 79 years of age. The incidence of early morning autoinflation in the combined group of adolescents and adults was 37.73% (Table 3).

As shown in Table 4, the incidence of middle ear effusion was significantly higher in children than in the older patients (87.09% versus 50.94%, $p < .05$).

In the older group the incidence of early morning autoinflation was significantly higher in cases with-

TABLE 2. EARLY MORNING AUTOINFLATION IN ATELECTATIC EARS IN THREE AGE GROUPS

		Presence of Morning Autoinflation	
Age Group (yr)	*No. of Atelectatic Ears*	*No. of Ears*	*%*
5-10	31	0	0
11-15	13	6	46.15
17-79	40	14	35.00
Total	84	20	23.80

TABLE 3. EARLY MORNING AUTOINFLATION IN ATELECTATIC EARS IN YOUNGER AND OLDER PATIENTS

Age Group (yr)	No. of Atelectatic Ears	*Morning Autoinflation* Present No.	Present %	Absent No.	Absent %
5-10	31	0	0	31	100.00
11-79	53	20	37.73	33	62.26
Total	84	20		64	

p<.05.

out middle ear effusion than in ears with effusion (46.15% versus 29.62%, p<.05; Table 5).

DISCUSSION

It is accepted today that a retracted tympanic membrane commonly is associated with relatively negative middle ear pressure.[6,7] It thus seems likely that the early morning hyperinflation or ballooning of the eardrum observed in this study in some ears is probably the result of a relatively positive intratympanic pressure.

That atelectasis and retraction pockets of the tympanic membrane is often not a static phenomenon has been shown by us previously.[5,8,9] However, while our previous reports describe fluctuations of the atelectatic eardrum and retraction pockets over a period of months or years, the present study demonstrates an "up-down" fluctuation within hours, ie, overnight. More than a third of the patients over the age of 10 presented an overnight fluctuation of their atelectatic ear.

The amount of air passing through the eustachian tube into the middle ear is considered to diminish during sleep, when swallowing frequency is reduced.[1] On the other hand, during sleep, blood oxygen was found to be lower than during the day,[10,11] hence its absorption from the middle ear should be increased. Both these phenomena should lead therefore to nocturnal middle ear negative pressure. However, this notion appears to be contradicted by the findings of Bylander et al[1] and of Hergils and Magnuson,[3] as well as by the results of this study, which can only be interpreted as indicating a higher middle ear pressure in the morning, on awakening, than on the previous evening.

TABLE 4. INCIDENCE OF MIDDLE EAR EFFUSION IN YOUNGER AND OLDER PATIENTS

Age Group (yr)	No. of Atelectatic Ears	*Ears With Effusion* No.	%
5-10	31	27	87.09
11-79	53	27	50.94
Total	84	54	

p<.05.

TABLE 5. CORRELATION BETWEEN MORNING AUTOINFLATION AND PRESENCE OF MIDDLE EAR EFFUSION IN OLDER AGE GROUP (11 TO 79 YEARS)

	No. of Atelectatic Ears	*Presence of Morning Autoinflation* No.	%
Ears without effusion	26	12	46.15
Ears with effusion	27	8	29.62
Total	53	20	

p<.05.

The disappearance of atelectasis and the ballooning of the drum in atelectatic ears after a night's sleep theoretically could be attributed to diffusion of elevated nocturnal blood carbon dioxide, as proposed by Bylander et al[1] and by Hergils and Magnuson.[3] However, in a previous study[12] we showed that atelectatic ears that were inflated (politzerized) with various gases returned to their original atelectatic condition after a time period that corresponded to the gas used and was in accordance with the laws of gas diffusion. Under these conditions CO_2, which has a high diffusion coefficient, was found to diffuse and return into the circulation from the middle ear within 5 minutes. On the other hand, atelectatic ears that were politzerized with air returned to their original atelectatic position after an average of 53 minutes, which is in line with the lower diffusion coefficients of the gases that constitute air, ie, nitrogen and O_2. The fact that it took the atelectatic ears that inflated spontaneously during the night 54.46 minutes on average to return to their original atelectatic condition would therefore exclude for all practical purposes the possibility that CO_2 by itself was the gas that filled these ears during sleep and returned into the circulation on awakening.

An interesting finding was the total absence of early morning autoinflation in children under the age of 11. This group also was characterized by a significantly higher prevalence of secretory otitis media than the older group (87.09% versus 50.94%, p<.05). Furthermore, among the older group, ears without an effusion exhibited a significantly higher prevalence of morning autoinflation than ears that contained fluid (46.15% versus 29.62%, p<.05). It thus appears that both age and the presence of middle ear secretion influence (negatively) the incidence of early morning autoinflation in atelectatic ears.

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SURGERY OF THE UPPER RESPIRATORY SYSTEM

A course entitled Surgery of the Upper Respiratory System will be held June 20-22, 1990, at the Harvard Medical School in Boston. For further information, contact Pamela Turner, Course Coordinator, c/o William W. Montgomery, MD, 100 Charles River Plaza, Boston, MA 02114; (617) 523-1607.

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FIFTH INTERNATIONAL SYMPOSIUM
RECENT ADVANCES IN OTITIS MEDIA

The Fifth International Symposium on Recent Advances in Otitis Media will be held May 20-23, 1991, at the Sheraton Bal Harbour in Bal Harbour, Florida. For further information, contact David J. Lim, MD, 4331 University Hospitals Clinic, 456 W Tenth Avenue, Columbus, OH 43210; Phone: (614) 293-8103; Fax: (614) 293-5506.

Ann Otol Rhinol Laryngol 99:1990

IMMUNOHISTOCHEMICAL EXAMINATION OF OLFACTORY MUCOSA IN PATIENTS WITH OLFACTORY DISTURBANCE

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The olfactory mucosa was examined by immunohistochemistry in patients with olfactory disturbance: anosmia due to choanal atresia and chronic sinusitis, early-stage common cold, late-stage common cold, and head trauma. The results indicate that the olfactory mucosa of patients with olfactory disturbance shows specific kinds of immunoreactive patterns and that immunohistochemistry is useful for examining the degree of degeneration of pathologic human olfactory mucosa and for clarification of prognosis.

KEY WORDS — biopsy, human olfactory mucosa, immunohistochemistry, olfactory disturbance.

INTRODUCTION

Systematic methods for morphologic examination of the human olfactory mucosa have been developed with light and electron microscopy.[1,2] In addition, biopsy of olfactory mucosa in patients with hyposmia and anosmia has been used recently for the diagnosis of olfactory disturbance.[3] We already have studied the changes present in olfactory mucosa in cases of hyposmia or anosmia using both light and electron microscopy[4] and immunohistochemistry.[5,6] The present paper describes new immunohistochemical findings on the olfactory mucosa in patients with olfactory disturbance.

MATERIALS AND METHODS

Materials. Human materials were obtained from ten patients without anesthesia by use of a special instrument (Nakano's forceps type 3). This instrument is used generally in our clinic and has been described in detail elsewhere.[6] Therefore, only a brief description is given here. The instrument is a stainless steel forceps 84 mm in length with a 4 x 1-mm blade and a 0.7-mm-deep cup of its tip. Among the ten patients with olfactory disturbance, one had anosmia due to acquired bilateral choanal atresia of 10 years' duration, two had chronic sinusitis of 25 and 40 years' duration, respectively, three had common colds (viral infection suspected), and one had head trauma. In the other three patients — a 58-year-old woman, a 56-year-old man, and a 46-year-old man — the anosmia and hyposmia were of unknown origin.

Immunohistochemical Staining. The specimens were fixed in Bouin's fluid for 2 hours, dehydrated in a graded ethanol series, and embedded in paraffin. Dewaxed sections were processed for the peroxidase-antiperoxidase (PAP) method. Neuron-specific enolase (NSE) and glia-specific S-100 protein (S-100) antisera (DAKO) were each used at a dilution of 1:900. Antiserum against human cytokeratin (CK, DAKO) was used at a dilution of 1:600. Reacted specimens were exposed to diaminobenzidine or aminoethylcarbazole for staining development.

Conventional staining controls, as recommended by Sternberger,[7] were used to check the specificity of the immunostaining. In addition, the antisera were preincubated with their corresponding antigens (10 to 15 μg/mL of diluted antiserum) for 24 hours at 4°C. The absorbed antisera did not show any immunoreactivity with the olfactory mucosa.

RESULTS

Choanal Atresia. Neuron-specific enolase immunoreactivity clearly was present in the dendrites and perikarya of the multilayered olfactory receptor cells in sufficiently thick olfactory neuroepithelium. Reactivity sometimes also was found in the olfactory vesicles located at the distal ends of dendrites. Supporting cells and basal cells showed no reaction to anti-NSE antiserum (Fig 1A). Immunoreactivity for S-100 was present in the ductal cells of Bowman's glands in the epithelium and acinar cells in the lamina propria. Olfactory nerve and trigeminal nerve bundles in the lamina propria gave the same positive reaction with anti-S-100 antiserum (Fig 1B). Intense CK immunoreactivity was seen in the perikarya of basal cells arranged regularly on the basement membrane (Fig 1C).

Chronic Sinusitis. Neuron-specific enolase immunoreactivity could be seen clearly in the dendrites and perinuclear region of receptor cells. Even thin epithelium had many NSE-reactive receptor cells (Fig 2A). Staining of the mucosa with anti-S-100 resulted in clear labeling of thin, tiny olfactory

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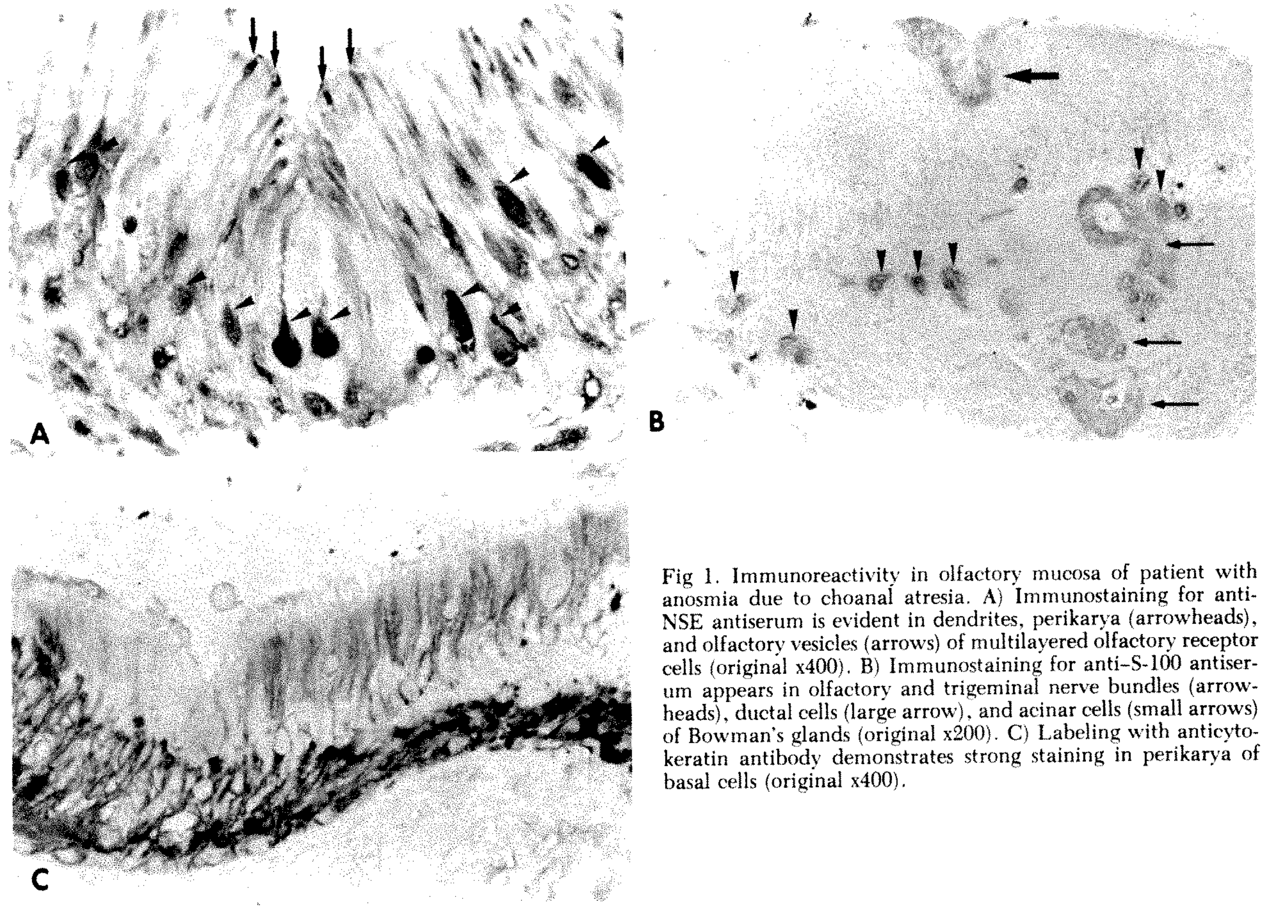

Fig 1. Immunoreactivity in olfactory mucosa of patient with anosmia due to choanal atresia. A) Immunostaining for anti-NSE antiserum is evident in dendrites, perikarya (arrowheads), and olfactory vesicles (arrows) of multilayered olfactory receptor cells (original x400). B) Immunostaining for anti-S-100 antiserum appears in olfactory and trigeminal nerve bundles (arrowheads), ductal cells (large arrow), and acinar cells (small arrows) of Bowman's glands (original x200). C) Labeling with anticytokeratin antibody demonstrates strong staining in perikarya of basal cells (original x400).

nerve axons that were ensheathed by Schwann cells near the basement membrane. Many Bowman's glands also reacted to anti-S-100 in the lamina propria (Fig 2B). Labeling with anti-CK antibody demonstrated a staining pattern similar to that seen in choanal atresia, indicating the distribution of CK in the perikarya of basal cells.

Common Cold (Viral Infection Suspected). There were clear differences between the early (20 days and 3 months after common cold) and the late (2 years after common cold) stages. In the early stage, NSE immunoreactivity was found in the dendrites and perikarya of a number of receptor cells (Fig 3A,B). The nerve bundles and Bowman's glands in the lamina propria were stained with anti-S-100 antiserum (Fig 3C). Cytokeratin immunoreactivity was found in the perikarya of regularly arranged basal cells (Fig 3D). In the late stage, on the other hand, there was no NSE reactivity in the epithe-

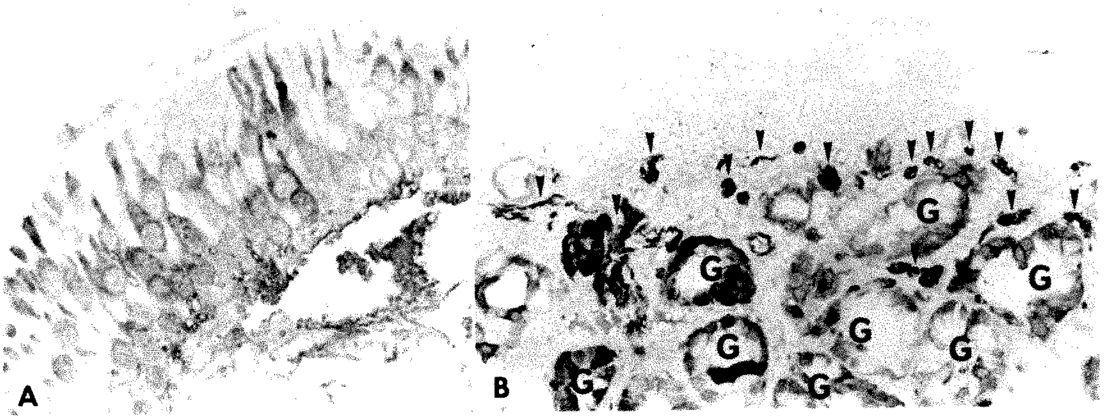

Fig 2. Immunoreactivity in olfactory mucosa of patient with anosmia due to chronic sinusitis. A) Many NSE-immunoreactive receptor cells can be seen in epithelium (original x400). B) S-100 immunoreactivity is found in thin olfactory nerve axons close to basement membrane (arrowheads) and Bowman's glands (G) (original x400).

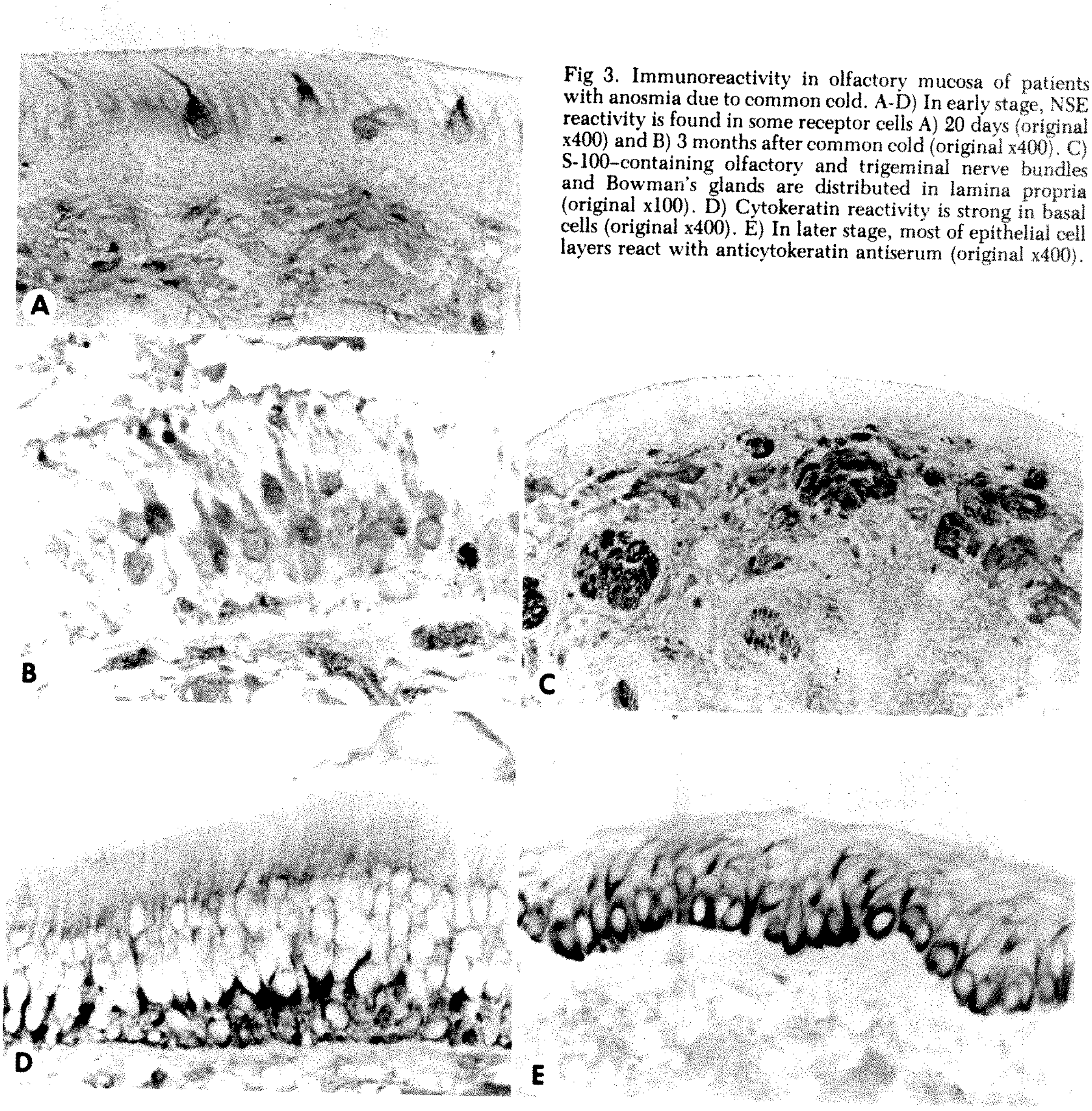

Fig 3. Immunoreactivity in olfactory mucosa of patients with anosmia due to common cold. A-D) In early stage, NSE reactivity is found in some receptor cells A) 20 days (original x400) and B) 3 months after common cold (original x400). C) S-100–containing olfactory and trigeminal nerve bundles and Bowman's glands are distributed in lamina propria (original x100). D) Cytokeratin reactivity is strong in basal cells (original x400). E) In later stage, most of epithelial cell layers react with anticytokeratin antiserum (original x400).

lium. Anti-CK antibody produced an extensive reaction in most cell layers of the epithelium, but a few cells did not react with anti-CK antiserum (Fig 3E). No S-100 immunoreactivity was found in the lamina propria.

Head Trauma. There were no NSE-reactive cells in the epithelium, but S-100 immunoreactivity was found in nerve bundles and Bowman's glands in the lamina propria (Fig 4A). Cytokeratin immunoreactivity was found in the perikarya of basal cells showing a pattern similar to that in choanal atresia and chronic sinusitis, but the cells situated in the upper layers did not react with anti-CK antiserum (Fig 4B).

Disturbance of Unknown Origin. Two kinds of immunoreactive pattern were seen in these three cases. In two cases, a number of NSE-reactive cells were observed in the epithelium (Fig 5A), and many S-100–reactive nerve bundles and Bowman's glands were present in the lamina propria (Fig 5B). Reactivity to anti-CK antiserum was found in the perikarya of basal cells (Fig 5C). In the other case, while NSE and S-100 immunoreactivities were not found in the epithelium, all epithelial cell layers of sufficient thickness showed a strong reaction to anti-CK antiserum (Fig 5D).

DISCUSSION

The human olfactory mucosa consists of the olfactory epithelium and lamina propria. The olfactory epithelium contains three fundamental cell types: supporting cells, olfactory receptor cells, and basal cells. In the lamina propria, there are olfactory and trigeminal nerve bundles, Bowman's glands, and small vessels. In cases of olfactory disturbance, these structures are destroyed and degeneration of the olfactory mucosa occurs. Morpho-

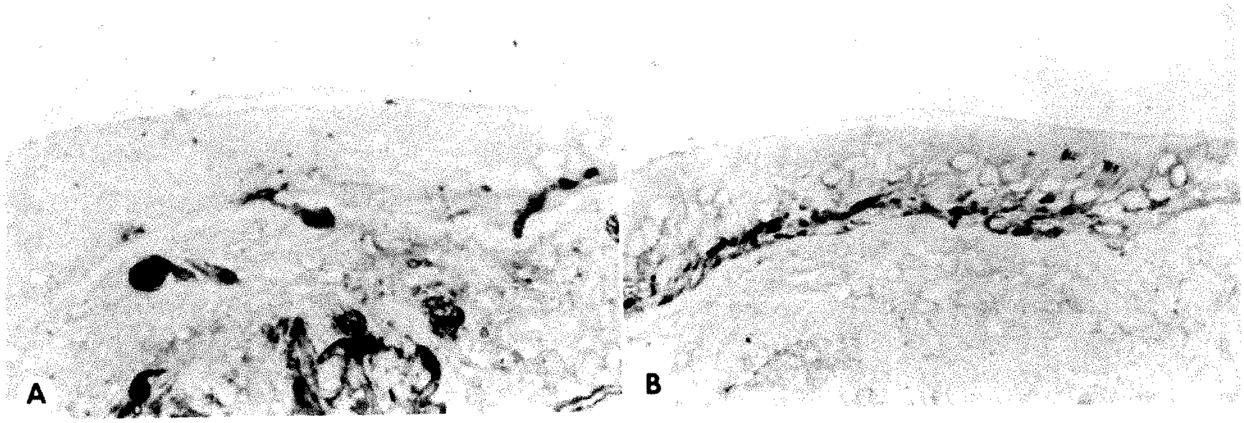

Fig 4. Immunoreactivity in olfactory mucosa of patient with anosmia after head trauma (original x200). A) S-100 reactivity of trigeminal nerve bundles and Bowman's glands is present in lamina propria. B) Regular cytokeratin reactivity is found in basal cells.

logic examination by light or electron microscopy can reveal changes in the epithelium to some extent, but does not allow determination of any residual olfactory function. To solve this problem, immunohistochemistry has been applied, resulting in confirmation that NSE, S-100, and CK are good markers of olfactory receptor cells, nerve bundles, Bowman's glands, and basal cells.[8]

Immunohistochemical study of the olfactory mucosa provides important information. Olfactory function may be impaired through pathologic changes in structure such as swelling of the respiratory mucosa near the olfactory cleft; damage to the olfactory cilia, olfactory vesicles, and cell bodies of receptor cells; and impairment of olfactory nerve axons, nerve bundles, and the upper olfactory tract above the olfactory bulb in the main olfactory pathway. Degeneration of Bowman's glands may cause a decrease in secretion. In these areas, immunohistochemistry combined with olfactory mucosal biopsy can be used to examine cell bodies of receptor cells and basal cells in the epithelium, olfactory nerves, and Bowman's glands in the lamina propria.

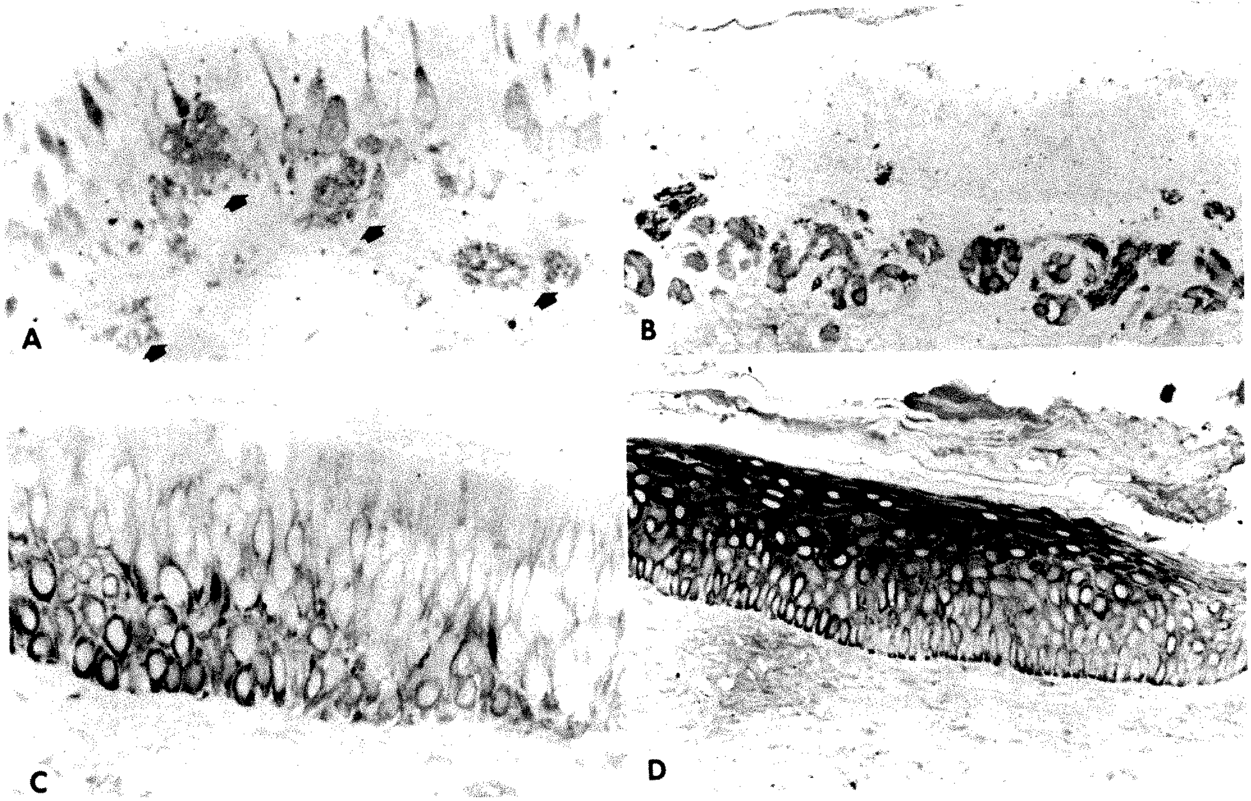

Fig 5. Immunoreactivity in olfactory mucosa of patients with anosmia or hyposmia of unknown origin. A-C) In two cases (A and C are same case), numbers of A) NSE-reactive cells (original x400; arrows — olfactory nerve bundles), B) S-100-reactive nerve bundles and Bowman's glands (original x200), and C) cytokeratin-reactive basal cells (original x400) are evident. D) In another case, strong reactivity to anticytokeratin antiserum is found in all epithelial cell layers (original x400).

In this study, various cases were examined according to the above viewpoints. In choanal atresia, many olfactory receptor cells, nerve bundles, Bowman's glands, and basal cells reacted to anti-NSE, anti-S-100, and anti-CK antisera. These results resemble those obtained in human fetuses and guinea pigs previously reported by us[8] and indicate that olfactory function might be preserved completely, without disuse atrophy. In fact, olfaction in this patient recovered to a normal level after surgery to restore the choana. The immunohistochemical findings in choanal atresia were used as normal control data when the olfactory mucosae of other patients were investigated.

In chronic sinusitis, as for choanal atresia, the same normal reactions to anti-NSE, anti-S-100, and anti-CK antisera were found, so it is assumed that olfactory function was preserved and that chronic inflammation had no deleterious effect on the olfactory mucosa. In the patient with a common cold, a number of functional olfactory receptor cells were preserved in the early period after loss of olfaction. However, these cells degenerated and disappeared gradually. Eventually the epithelium became atrophic and thin, resembling squamous metaplasia in the late stage. Various reports have described the changes occurring in the olfactory epithelium after viral infection. Douek and Bannister[9] reported that the olfactory epithelium was replaced with respiratory epithelium, and Twomey et al[10] observed that the olfactory epithelium was covered by nonkeratinizing stratified squamous epithelium. Our present findings resembled those of Twomey et al, but there was a difference in that a few supporting cells that did not react with anti-CK antiserum remained in the epithelium. In head trauma, no NSE-immunoreactive cells could be seen in the epithelium, and only basal cells reacted with anti-CK antiserum. The cells situated in the upper layer showed no reaction with anti-NSE and anti-CK antisera. These cells may be supporting cells, since it has been reported that when olfactory nerves are transected completely, olfactory receptor cells disappear, but supporting cells and basal cells remain intact.[4] Nerve bundles that reacted with anti-S-100 antiserum in the lamina propria may have been trigeminal nerve bundles. In the patients whose olfactory disturbances were of unknown origin, two kinds of epithelium were seen. Two patients had a number of functional receptor cells, but the other did not. Only CK immunoreactivity was found throughout the epithelium, indicating that the neuroepithelium had been replaced by stratified squamous epithelium. These findings reveal that olfactory disturbance of unknown origin shows different degrees of degeneration due to other causes.

The specimens examined in this study revealed a systematic degenerative course in impaired olfactory neuroepithelia. Briefly, in the first stage, a decrease in functional receptor cells occurs. Second, the receptor cells disappear, and only supporting cells and basal cells remain. Third, all the epithelium is replaced by squamous cells that have developed from basal cells. In the terminal degenerative stage of human olfactory mucosa, no cells in the epithelium react with anti-NSE antiserum, no olfactory nerve bundles react with anti-S-100 antiserum in the lamina propria, and all epithelial cell layers react with anti-CK antiserum immunohistochemically.

Next, regeneration of olfactory receptor cells should be mentioned. It has been reported in animal experiments that following the loss of adult receptor neurons through physical or chemical damage, new neurons are regenerated through proliferation and differentiation of precursor basal cells within 1 or 2 months.[11,12] In the present human cases, it was unclear whether olfactory receptor cells regenerated after degeneration. In the cases of common cold and head trauma and in one case of disturbance of unknown origin, regeneration did not occur. These results suggest that olfactory receptor cells in humans do not regenerate if they are damaged severely. Even if basal cells remain, they develop into keratinizing squamous cells.

There are various opinions concerning the propriety of olfactory mucosal biopsy, and so the indications for this technique should be considered. As the relative safety of this type of biopsy already has been confirmed by many studies, the most important problem is whether the condition of the epithelium can be determined from a small specimen. Nakashima et al[2] reported that degeneration of the human olfactory mucosa could occur without olfactory disturbance; thus, biopsy had no usefulness. There is certainly a danger in assessing the function of the olfactory mucosa on the basis of H & E staining alone. Even when the epithelium appeared atrophic and thin, as in chronic sinusitis, many NSE-reactive receptor cells were found to remain when examined by immunohistochemistry. It is conceivable that there is no relationship between actual olfactory function and the results of H & E staining, even when they indicate degeneration. The function of the olfactory mucosa therefore should be evaluated not only by H & E staining, but also by immunohistochemical findings. Olfactory mucosal biopsy may be a useful method if immunohistochemistry, which should be considered for examination of receptor cells, basal cells, olfactory nerves, and Bowman's glands, also is performed.

CONCLUSION

This study demonstrated the usefulness of immunohistochemistry for examining the function and structure of the human olfactory mucosa. It was helpful for the diagnosis of olfactory disturbance and determining the prognosis when combined with olfactory mucosal biopsy.

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QUANTITATION OF TUBOTYMPANAL MUCOCILIARY CLEARANCE IN OTITIS MEDIA WITH EFFUSION

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In an attempt to analyze the tubotympanal mucociliary function in otitis media with effusion (OME), human serum albumin labeled with technetium 99m was instilled into 36 ears with effusion and 16 without. The clearance function of the tubotympanum was measured quantitatively. The viscoelasticity of the effusions was measured and was compared with the clearance rate. The clearance rate was significantly lower in ears with effusion than in those without. A significant negative correlation was observed between clearance rate and dynamic viscosity at dynamic viscosities above 2 poise. It is concluded that ears with effusion have significantly lower mucociliary clearance than those without, and that the viscosity of the effusions plays an important role in the mucociliary dysfunction in OME.

KEY WORDS — elasticity, middle ear effusion, mucociliary clearance, otitis media with effusion, viscosity.

INTRODUCTION

It has been reported that the mucociliary clearance function is impaired in chronic otitis media with effusion (OME),[1] but previous reports have indicated only that the clearance function was missing in OME, giving no further information as to the severity or the specific location of dysfunction. Although many factors are postulated as the possible causes of mucociliary dysfunction, such as abnormal rheologic properties of effusions[2] and ciliary damage,[3] no one has ever shown which of these factors is responsible for mucociliary dysfunction in vivo. In order to answer these questions, it is necessary to measure the clearance function quantitatively and to compare the results with other parameters such as rheologic properties of the effusions.

A method using radioisotopes now is used widely in diagnosis of various diseases because of its accuracy and objectivity of measurement. This method provides information on both the structure and function of the organs. Recently, this method has been used for the measurement of the clearance function of the tubotympanum.[4,5] By using this method, we evaluated the tubotympanal mucociliary clearance and analyzed the results quantitatively. The relationship between mucociliary clearance and the rheologic properties of the middle ear effusions also was analyzed.

MATERIAL AND METHODS

Subjects. Fifty-two ears of 34 children 4 to 15 years of age (mean ± SD, 6.5 ± 2.1) were used in this study and were divided into 36 ears with effusion and 16 without effusion. The overall group consisted of children suffering from OME as diagnosed by clinical symptoms, pneumatic otoscopy, pure tone audiometry, and tympanometry; and effusions were identified by myringotomy. The ears of the latter group of 16 had previously retained effusion and had been followed up as having OME, but no effusion was detected on myringotomy. Informed consent for the study was obtained from the parents of the subjects.

Measurement of Clearance Function. With use of topical anesthesia, myringotomy was performed in the anterior-inferior quadrant. Middle ear effusions, if present, were aspirated with the Juhn Tym-Tap and stored at 4°C for the measurement of their viscoelastic properties. With the subjects in the sitting position, 10 μL of sterile human serum albumin (HSA) labeled with technetium 99m (Midorijuji Company, Tokyo) was introduced into the middle ear cavity through a myringotomy incision by means of a microliter syringe. The HSA was placed into the hypotympanum. The radioactivity of 10 μL of HSA was 20 to 30 μCi, according to measurement by an isotope calibrator.

With the subject seated and the head fixed in the normal position, the tracer substance was detected by a gamma camera (Toshiba, model GCA-202, Tokyo) from above the head of the subject. The subjects were advised to swallow every minute. When a large amount of HSA entered the eustachian tube and nasopharynx during a swallowing, those subjects were excluded from the study, because we suspected muscular clearance. The sequential scintigrams were taken at intervals of 30 seconds and were recorded in the computer for the following analysis. The radioactivity of the tympanic cavity was counted in every sequential scintigram, and the radioactivity of this region, as a percentage of the initial radioactivity, was plotted against time.

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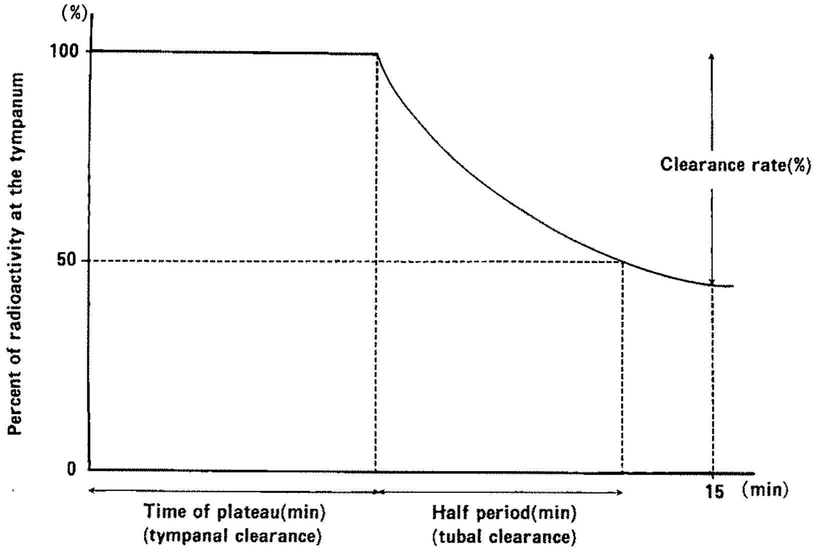

Fig 1. Schematic illustration of clearance curve and analysis of curve by three indices: clearance rate, time of plateau, and half period. Clearance rate indicates whole tubotympanal clearance. Time of plateau and half period indicate tympanal and tubal clearance, respectively.

Analysis of Clearance Curve. When the tracer was transported, most of the curves were similar to that shown in Fig 1. At first a plateau was observed and was followed by a rapid fall. The decrease of the radioactivity was almost exponential. Three indices were used to evaluate the curve. First, the clearance rate is defined as the percentage of radioactivity decreased in the tympanic cavity in 15 minutes.

Second, the time of plateau is defined as the length of time until the onset of the rapid fall of radioactivity. The onset of transport was determined when the transport from the tympanic cavity was recognized for the first time on the sequential scintigram.

Third, to express the slope of the curve, the half period is defined as the length of time taken for the radioactivity at the onset of clearance to be reduced by half. The half period was calculated as follows. The radioisotopic counts after the onset of transport were plotted on semilogarithmic paper with time on the abscissa. A straight line was drawn to give the best fit through the slope. The half period ($T^{1/2}$) was calculated by the following equation.[6]

$$T^{1/2} = \frac{\log_{10} 2}{m}$$

where m is the slope of the straight line. The half period was examined only in ears that transported the HSA from the tympanic cavity within 15 minutes.

Measurement of Viscoelasticity. The elastic modulus (G′) and the dynamic viscosity (η') of the effusions were measured with an oscillating sphere magnetic rheometer within 4 hours after the collection of samples. Details of this instrument are described elsewhere.[7,8] The G′ is indicative of elastic behavior, and the η' is a measure of viscous behavior. All the measurements were made at 25°C at the frequency of 1 Hz.

Statistical Analysis. The Wilcoxon test was used to examine the difference in clearance rate. The χ^2 test was used to compare the length of the time of plateau. The test for correlation was carried out by the method of least squares.

RESULTS

Clearance Rate. The median of the clearance rate was 5% in the ears with effusions, and 20.7% in those without (Fig 2A). The difference was statistically significant ($p<.05$).

Time of Plateau. When no transport was observed within 15 minutes, the time until onset was determined as more than 15 minutes (Fig 2B). The time of plateau was more than 15 minutes in 61% of the ears with effusion and in 12% of those without effusion. The difference between the two groups was statistically significant ($p<.01$).

Half Period. The half period was examined in 14 ears with effusion (39%) and in 14 ears without effusion (88%). The median of the half period was 33.2 minutes in the ears with effusion and 29.8 minutes in those without effusion (Fig 2C). No significant difference was observed between the two groups.

Viscoelasticity of Effusion Versus Clearance Rate. The viscoelasticity was measured in 33 ears with effusion. The G′ at 1 Hz ranged from 1 to 27,000 dyne/cm^2, and the η' at 1 Hz ranged from 0.2 to 1,790 poise. No significant correlation was observed between the G′ of the effusions and the clearance rate. The relation between the η' of the effusions and the clearance rate is shown in Fig 2D. Above an η' of 2 poise, the negative correlation between the clearance rate and the η' was significant ($r=-0.3572$, $p<.05$). The value of 2 poise was determined because the optimal η' value for mucociliary clearance rate was about 2 poise, and there is a positive correlation below an η' of 2 poise and a negative correlation above an η' of 2 poise in vitro.[9]

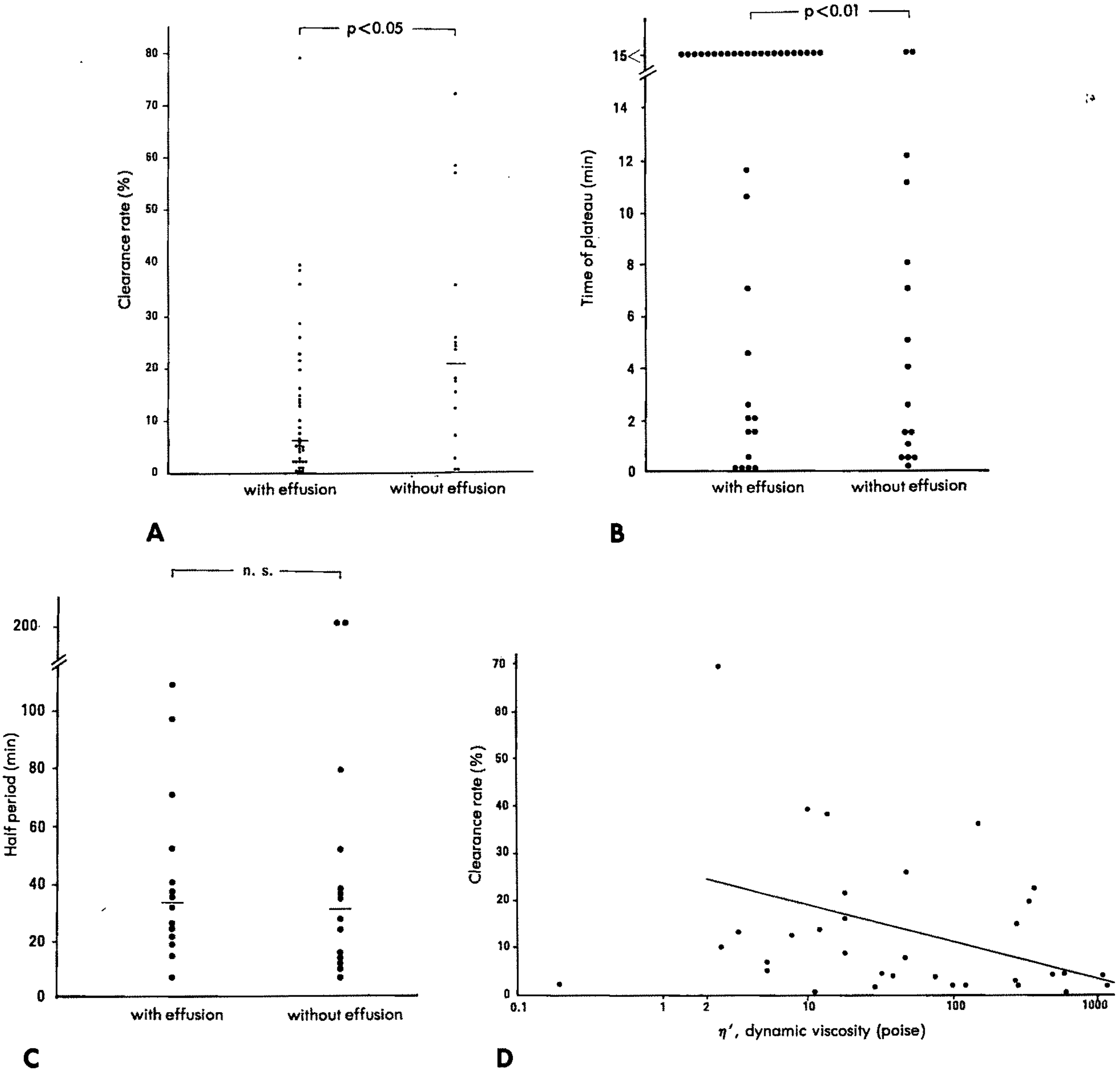

Fig 2. Results. A) Clearance rate in ears with effusion and in those without effusion. Rate is significantly lower in ears with effusion ($p < .05$). B) Time of plateau. Note longer time required for ears with effusion to start transporting tracer than for those without effusion ($p < .01$). C) Half period. No significant difference is observed in efficacy of tubal clearance between ears with effusion and those without effusion. D) Viscosity (η') of middle ear effusions versus clearance rate. Significant negative correlation is observed above η' of 2 poise ($r = -0.3572$, $p < .05$).

DISCUSSION

Two eliminative functions, muscular and ciliary, make up the tubotympanal clearance. Although a larger amount of effusion is expelled within a limited time period by the muscular clearance than by the ciliary one,[10] it is believed that the muscular clearance does not take place under the negative pressure in the middle ear cavity such as in OME.[11] Thus we focused on tubotympanal mucociliary clearance in the present study. Only 10 μL of HSA was instilled into the tympanic cavity in order to minimize the interference of muscular clearance, since it is reported that a larger amount of HSA is likely to be eliminated by muscular clearance.[1] We had used various doses of HSA and found that the smaller the amount of tracer, the less frequently muscular clearance occurs. However, muscular clearance can occur even if 0.01 mL is used. So we excluded suspected cases of muscular clearance from the study. We measured the clearance function for 15 minutes, because the children could not tolerate longer testing.

The clearance rate, which was the index of the tubotympanal mucociliary clearance, was significantly lower in the ears with effusion than in those without effusion. The ears in the latter group had retained the effusion previously, but did not have detectable effusion on follow-up. In this sense, these ears are not always normal control ears, but they could be regarded as ears in the process of recovery. In 61% of the ears with effusion, the clearance was totally absent, but the remaining 39% of the ears showed various clearance rates. This shows that the mucociliary system is impaired to various degrees in OME.

In order to clarify the causes of mucociliary dysfunction in OME, we compared the clearance rate with the G' and η' of the effusions. The mucociliary transport is governed by three major factors: mucus, cilia, and the interaction between them. Impairment of any of these three factors results in a dysfunction of mucociliary transport. The rheologic qualities of the mucus are involved in the mucus factor. It is known that the mucociliary transport rate depends on both the G' and η' of the effusions in vitro.[9] Although no significant correlation was observed between the G' and the clearance rate, a significant negative correlation was observed between the η' and the clearance rate in this study. These results suggest that the η' of the middle ear effusions is one of the important factors in the mucociliary dysfunction in this disease.

In the present study, most of the clearance curves showed plateaus before the transport started. Interestingly, once the tracer was transported into the tympanal orifice, it was transported through the eustachian tube to the nasopharynx without interruption in all cases, as shown on the scintigrams. These observations led us to realize that the tracer substances would not enter the tympanal orifice of the eustachian tube in the ears in which transport did not take place. Thus, we employ the time of plateau as an index showing the mucociliary clearance function of the tympanic cavity. The significant difference in the time of plateau between the two groups suggests a lowered mucociliary function in the tympanic cavity in the ears with effusion. Thus, the tympanic cavity may be a site responsible for mucociliary dysfunction in OME.

Since the tubal clearance was not tested for those ears that did not transport the tracer to the eustachian tube, no conclusion can be drawn from the comparison of the half periods of the two groups in this study. However, the half period indicates the efficacy of tubal clearance. The tubal clearance can be evaluated only when the tracer reaches the tympanal orifice of the eustachian tube.

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MORPHOLOGY OF SYNAPSES AT THE BASE OF HAIR CELLS IN THE ORGAN OF CORTI OF THE CHIMPANZEE

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The synaptic morphology of inner and outer hair cells of the organ of Corti of the chimpanzee was evaluated by serial section electron microscopy. The morphology of nerve terminals and synapses at both sites was very similar to that of human and other mammalian species. Two types of nerve terminals, nonvesiculated and vesiculated, with distinct synaptic morphology were found. In addition, between some nonvesiculated endings and outer hair cells, a reciprocal synaptic relationship was seen. In such terminals there was morphologic evidence for transmission from hair cell to neuron and from neuron to hair cell between a single neuron and an outer hair cell.

KEY WORDS — hair cell, organ of Corti, synapse.

INTRODUCTION

Two types of nerve endings, differentiated in part by their synaptic specialization, have been described at the base of outer hair cells[1-5] in the organ of Corti of all mammalian species studied. The type 1, or nonvesiculated ending, assumed to be the neural terminal of an afferent fiber, is characterized by the presence of presynaptic and postsynaptic membrane thickening and, in most species, a presynaptic ribbon or body surrounded by synaptic vesicles on the hair cell side of the synapse. The type 2, or vesiculated ending, assumed to be the neural terminal of the olivocochlear efferent bundle, is characterized by the presence of many presynaptic vesicles within the nerve terminal and a subsynaptic cisterna within the outer hair cell and apposed to the subjacent limiting membrane. A reciprocal synaptic relationship between a neuron and an outer hair cell has been described in the human.[6] This was defined as the presence of two distinct types of synaptic specialization between a single nonvesiculated nerve terminal and an outer hair cell. The two types of synaptic specializations were similar to the afferent and efferent synapses previously described, thus suggesting a reciprocal synaptic relationship between the neuron and hair cell. Although reciprocal synapses have been found in the CNS,[7-9] retina,[10] carotid body receptor,[11] and the crista ampullaris of the frog,[12,13] they have not been found previously in the normal organ of Corti of any species other than human.

This study will demonstrate the typical synaptic morphology at the base of inner and outer hair cells and the presence of reciprocal synapses at the base of outer hair cells of all three rows in the chimpanzee.

MATERIALS AND METHODS

The temporal bones of an adult chimpanzee were received from the Yerkes Regional Primate Research Center. This 56-year-old female chimpanzee was killed humanely and painlessly while moribund from terminal myocardial disease. During life, the animal was involved in a number of behavioral studies. There was no history of significant noise exposure or ear disease. Fifteen years prior to death, the animal was treated with 2 g streptomycin and 0.5 g kanamycin for pulmonary tuberculosis. With use of deep pentobarbital anesthesia the head was perfused via carotid catheterization with 8% paraformaldehyde and 0.1% glutaraldehyde in 0.05 *M* phosphate buffer at pH 7.4. The temporal bones were removed and immersed in the same fixative following autopsy. Following fixation, the left temporal bone was decalcified in trichloracetic acid, dehydrated in graded alcohols, and embedded in celloidin. Serial sections were taken in the horizontal plane (parallel to the floor of the middle fossa) at a thickness of 20 μm. The cochlea and spiral ganglion were reconstructed in two dimensions by the method of Schuknecht.[14] The loss of neurons in each

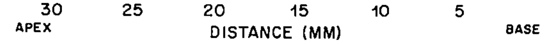

Fig 1. Histogram of cell loss of right ear of chimpanzee by cochlear location. Cell loss is represented in black; full height of bar represents 100%. IHC — inner hair cells, OHC — outer hair cells, vasc — vascularis.

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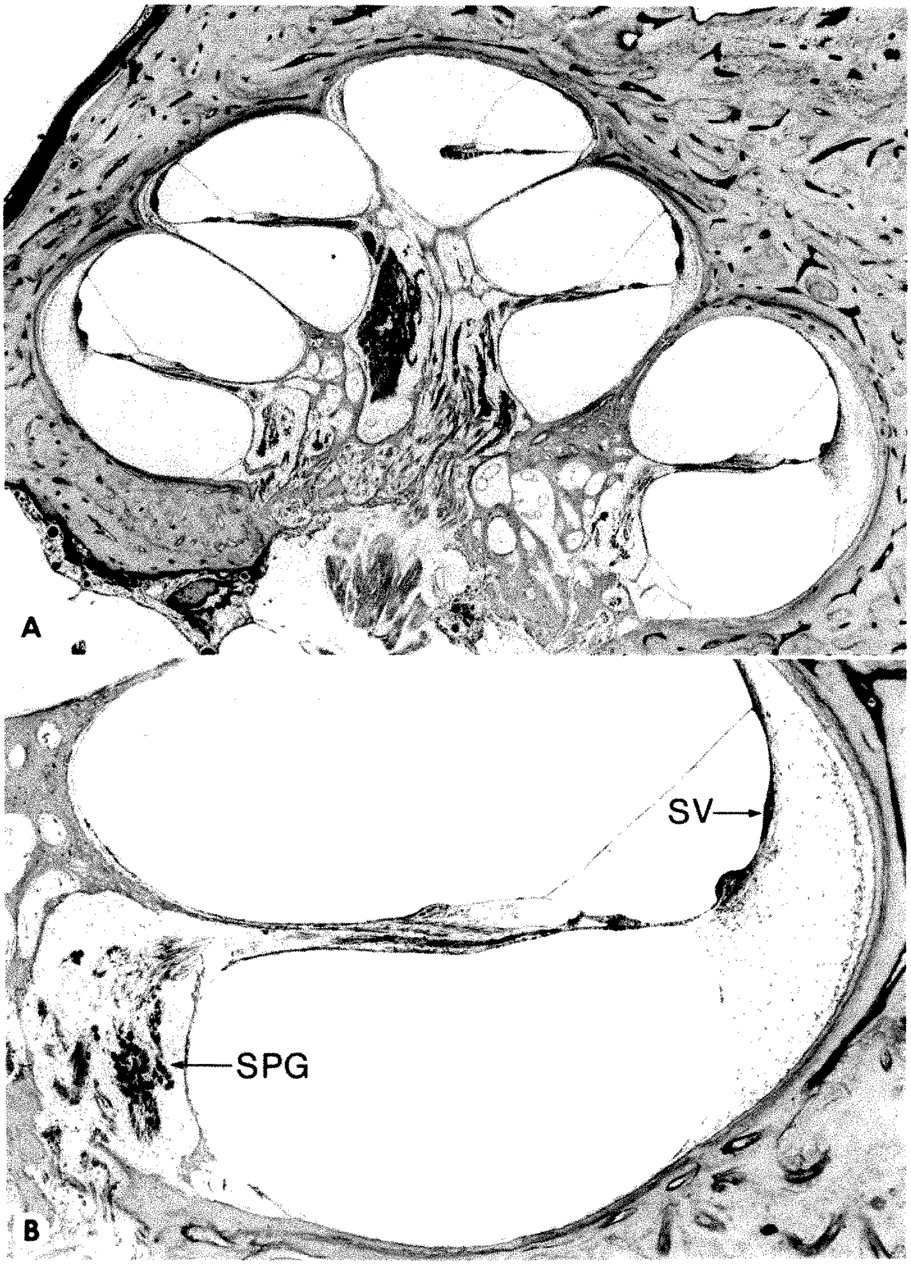
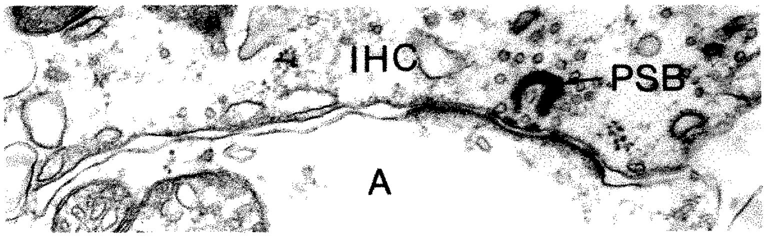


Fig 2. Organ of Corti of right ear of chimpanzee. A) Midmodiolar section (original x28). B) Higher-power micrograph of basal turn (original x87). There was moderate degeneration of stria vascularis (SV) and spiral ganglion (SPG).

segment of the spiral ganglion was estimated by extrapolation of counts in every tenth section.[15] On calculating a percentage loss (Fig 1), because of the lack of normative data for the chimpanzee, counts for the normal human spiral ganglion were used.[16]

The right temporal bone was prepared for electron microscopy. The mastoid was removed with rongeurs, and the otic capsule was thinned with a power drill before decalcification in 0.1 *M* disodium ethylenediaminetetraacetic acid (EDTA) with 2% glutaraldehyde in 0.1 *M* phosphate buffer.[17] The cochlea was sectioned, and the turns were separated and divided into 1- to 2-mm segments. After rinsing in 0.1 *M* phosphate buffer, the tissue blocks were postfixed in 2% osmium tetroxide in 0.1 *M* phosphate buffer for 2 hours. The tissue was stained en bloc with aqueous uranyl acetate for

Fig 3. Typical synapse between inner hair cell (IHC) and nonvesiculated neuronal ending (A) in middle turn (20 to 22 mm) (original x45,000). Synaptic morphology was marked by presynaptic and postsynaptic membrane thickening in presence of presynaptic body with surrounding vesicles (PSB).



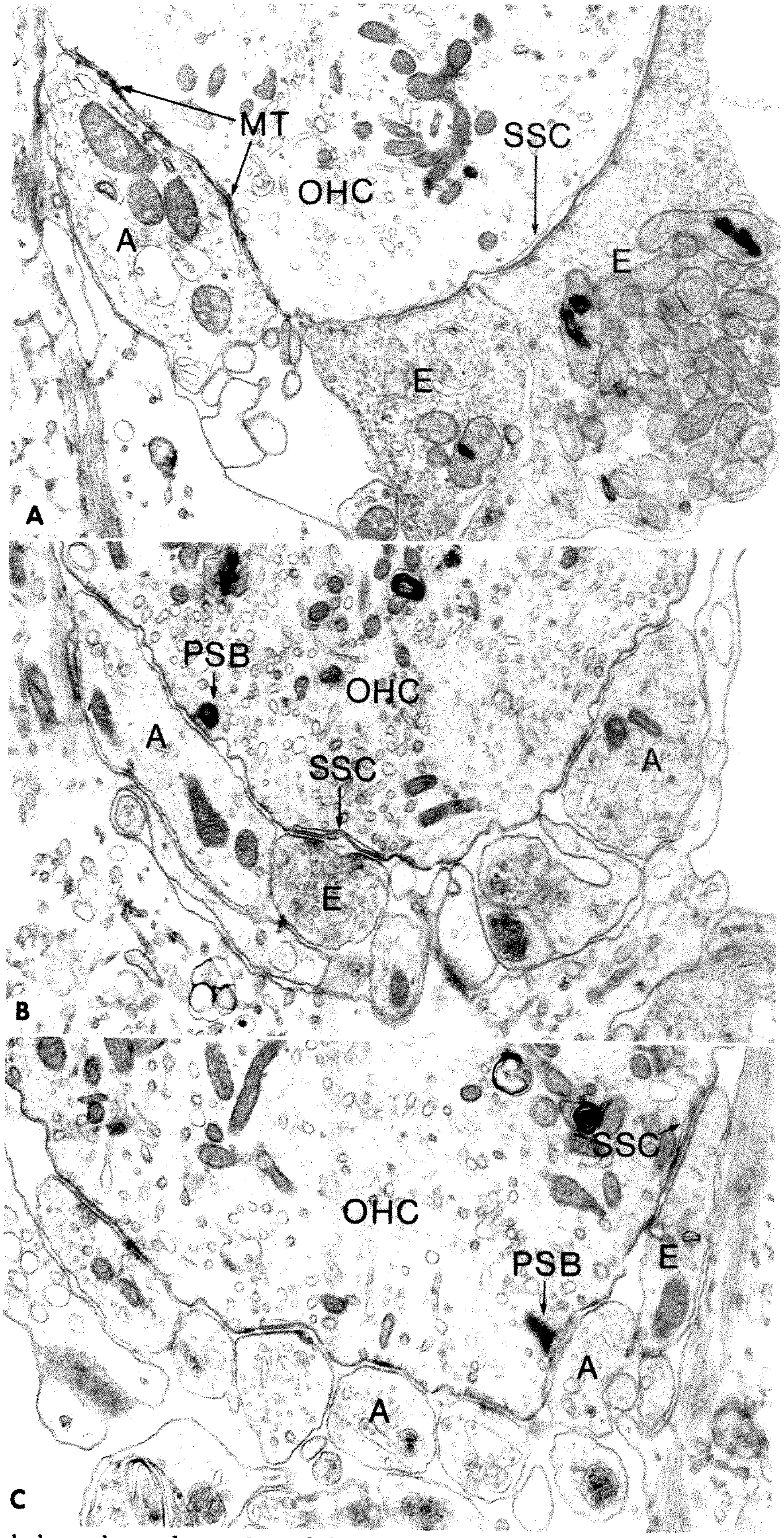


Fig 4. Synaptic poles of outer hair cells (OHCs). A) First row in basal turn (15 to 16 mm) (original x18,900). Two types of nerve terminals, nonvesiculated (A) and vesiculated (E), are seen. Synaptic specialization between nonvesiculated ending in hair cell consisted of membrane thickening (MT). Synaptic specialization between OHC and vesiculated endings consisted of subsynaptic cisterna (SSC). B) Second row in middle turn (20 to 22 mm) (original x22,000). Both nonvesiculated (A) and vesiculated (E) nerve terminals are seen. Presynaptic body (PSB) is seen apposed to nonvesiculated ending, and SSC is seen apposed to vesiculated nerve terminal. C) Third row in upper basal turn (16 to 18 mm) (original x29,000). Several small nerve terminals are seen at base of OHC. PSB is shown apposed to one nonvesiculated ending (A), and SSC is demonstrated apposed to presumed efferent ending (E).

2 hours, dehydrated in graded alcohols, exchanged with propylene oxide, and embedded in Epon. Thick sections were stained with 1% toluidine blue O, and thin sections were stained with lead citrate. Electron micrographs were taken with use of the JEOL 100 electron microscope. For the serial sec-

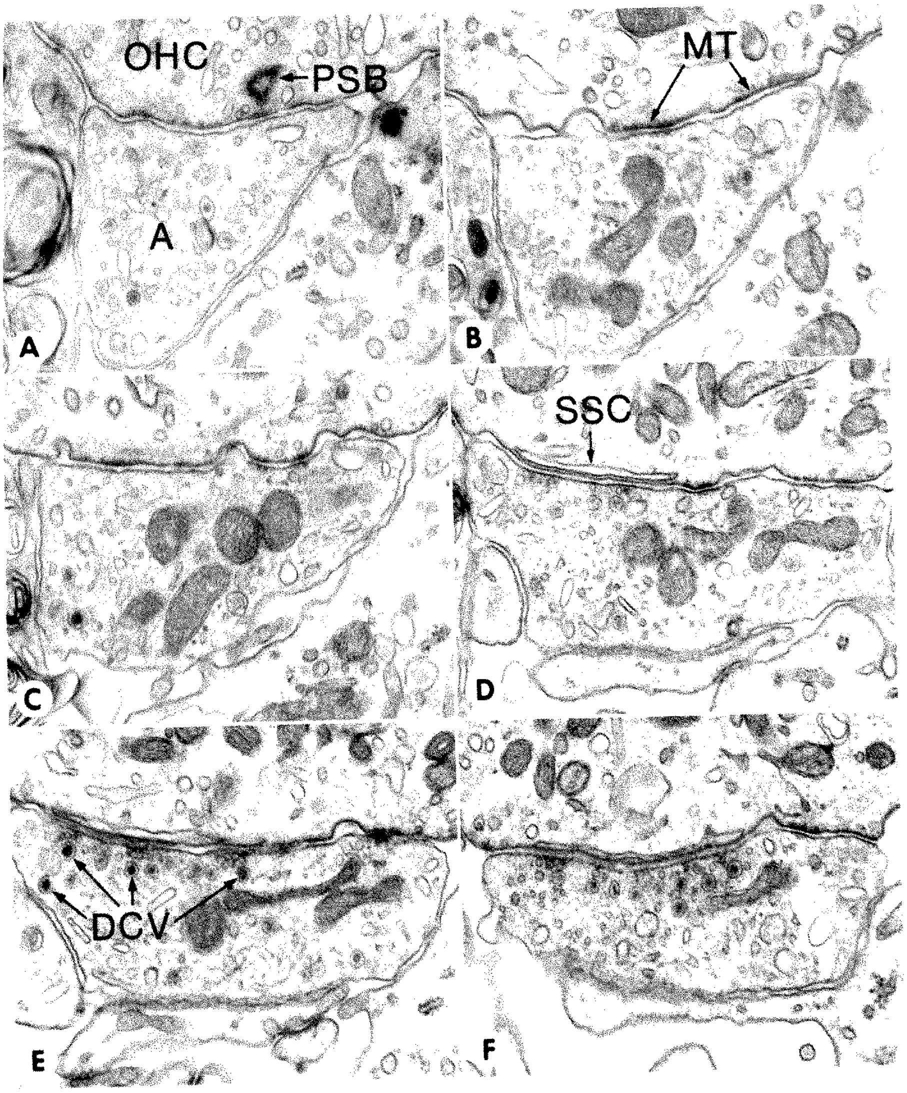


Fig 5. A-F) Selected serial sections of outer hair cell (OHC) of second row in basal turn (14 to 16 mm) (original x32,600). Nerve terminal (A) demonstrates synaptic specialization including membrane thickening (MT) and presynaptic body (PSB) suggestive of afferent synaptic relationship. In addition, in D through F, subsynaptic cisterna (SSC) and vesicles including dense core vesicles (DCVs) are seen, suggesting efferent-like synaptic relationship between OHC and same neuron. There were three sections between A and B, two sections between B and C, six sections between C and D, three sections between D and E, and five sections between E and F.

tion series, there were 260 serial sections viewed in the middle turn (20 to 22 mm) and 110 sections in the basal turn (15 to 16 mm).

RESULTS

There was no abnormality of the otic capsule, mastoid, or middle ear. The morphology of the inner ear was strikingly similar to that in the human. The length of the cochlear duct in the right ear as determined by serial section reconstruction was 30.3 mm. A midmodiolar section of the organ of Corti is shown in Fig 2, and a histogram of cell loss as determined by serial section reconstruction is shown in Fig 1. There was moderate to severe degeneration of the stria vascularis in all turns. There was no loss of inner hair cells, and loss of outer hair cells occurred only in the basal 5 mm of the cochlea. There was moderate loss of spiral ganglion cells in the basal turn as judged by comparison with human spiral ganglion. The total number of spiral ganglion cells was approximately 23,000 in the left ear.

SYNAPTIC MORPHOLOGY

Inner Hair Cell. A typical synapse between an inner hair cell and a presumed afferent neuron is shown in Fig 3. Synaptic thickening and a presynaptic body surrounded by vesicles, strikingly similar to that found in the human, were demonstrated.

Outer Hair Cell. The typical synaptic morphology of outer hair cells of the first, second, and third rows, respectively, is shown in Fig 4. Most neural terminals were of two types, consistent with other mammalian species. Nonvesiculated, presumably afferent endings possessed synapses with outer hair cells consisting of thickening of the apposed synaptic membranes greater on the presynaptic side. Some, but not all synaptic specializations also demonstrated a presynaptic body (Fig 4C). Vesiculated, presumably efferent endings demonstrated synapses with outer hair cells characterized by a subsynaptic cisterna in the cytoplasm of the outer hair cell juxtaposed to the nerve terminal. Efferent terminals seemed to be larger and more numerous in the first row of outer hair cells than in the second and third rows, as shown in Fig 4.

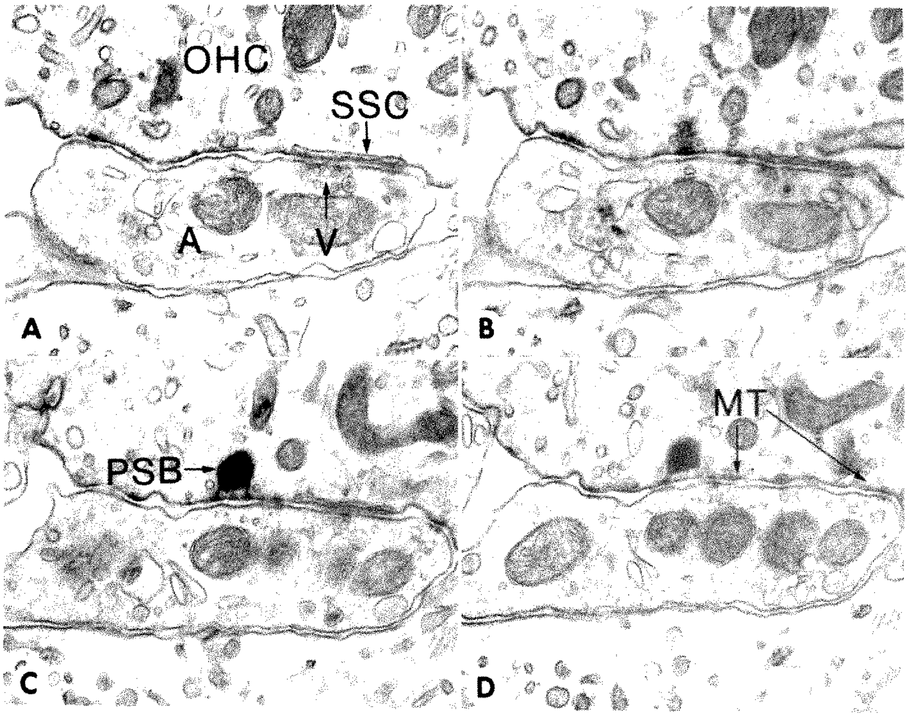


Fig 6. A-D) Selected sections from serial section reconstruction of synaptic pole of outer hair cell (OHC) of third row of upper basal turn (16 to 18 mm) (original x3,500). Nonvesiculated nerve terminal (A) demonstrates subsynaptic cisternae (SSC) and vesicles (Vs) suggesting efferent-like synaptic relationship, and presynaptic body (PSB) and membrane thickening (MT) suggest afferent-like synaptic relationship between OHC and same nerve terminal. Sections are serial with exception of one section between B and C.

Reciprocal Synapses. Examples of a reciprocal synaptic relationship between a single nonvesiculated ending and an outer hair cell are shown in Figs 5 and 6. In each case the nerve terminal was largely nonvesiculated and demonstrated thickening of apposed synaptic membranes and a presynaptic body, typical of an afferent synapse. In addition, as demonstrated by serial section electron microscopy, there was a small collection of vesicles, including dense core vesicles, in the cytoplasm of the nerve terminal adjacent to the outer hair cell and a subsynaptic cisterna in the subjacent cytoplasm of the outer hair cell, giving the appearance of a small efferent-like synapse. Reciprocal synapses were formed in all three rows of outer hair cells. The data were insufficient for us to estimate the incidence of reciprocal synapses among afferent endings.

DISCUSSION

The morphology of the mastoid, middle ear, and inner ear of the chimpanzee was extremely similar to that of the human. By serial section electron microscopy of the synaptic poles of inner and outer hair cells, the morphology of afferent and efferent endings was also similar to that described in the human,[18,19] although the number of afferent synapses with presynaptic bodies appeared to be less. Reciprocal synaptic relationships, identical to those previously described at the base of outer hair cells in humans,[6,20] were found at the base of outer hair cells of all three rows in the chimpanzee. The morphology of the nerve fibers involved in a reciprocal synaptic relationship with the outer hair cell was consistent with a nonvesiculated afferent fiber and demonstrated synaptic specialization also consistent with an afferent fiber, although the neural origin of such fibers is not known. In addition, a second synaptic specialization, characterized by synaptic vesicles on the nerve fiber side and a subsynaptic cisterna on the hair cell side, suggestive of a small efferent-like synapse, was seen between the same neuronal ending and an outer hair cell. Reciprocal synaptic relationships have been found between opposed dendrites in the CNS,[7-9] retina,[10] carotid body,[11] crista ampullaris of the frog,[12] and macula sacculi of the rat.[13] The possibility of a reciprocal synaptic relationship was previously described in the basilar papilla in the chicken[21] and between saccular hair cells and nerve terminals in mice.[22] However, in both of these instances the character of the nerve terminal subjacent to the hair cell was more consistent with a vesiculated efferent ending than an afferent terminal as shown in this study. In addition, both authors implied that the finding was rare in these species. An apparent reciprocal synaptic relationship between outer hair cells and afferent nerve terminals was induced by section of the olivocochlear bundle of the newborn kitten.[23] Reciprocal synapses were not found in the normal cat or when the olivocochlear bundle was sectioned in the adult cat. The authors interpreted these as "aberrant" postsynaptic cisternae at the base of outer hair cells and as evidence that efferent fibers normally cause regression of the number of afferent endings on outer hair cells during development.

In the human,[20] approximately 56% of outer hair cells of the organ of Corti demonstrated reciprocal synapses. The incidence of reciprocal synapses increased from the first to the third rows of outer hair cells. Although data are not yet available concerning the incidence of reciprocal synapses in the chimpanzee, they were easily found in relatively small series of serial sections, again suggesting that these structures are not rare.

The possible function of reciprocal synapses can only be speculative. Their presence only at the base of outer hair cells, which have a strongly divergent innervation (that is, with few neurons innervating many hair cells), suggests the possibility of a feedback loop between outer hair cells sharing a common dendritic innervation. The finding of such reciprocal synapses only in the human and chimpanzee and not in other mammalian species studied to date suggests recent phylogenetic development of this pattern of innervation.

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INCREASED GLIAL FIBRILLARY ACIDIC PROTEIN IMMUNOREACTIVITY IN ASTROCYTES WITHIN THE LATERAL VESTIBULAR NUCLEUS OF THE CAT FOLLOWING LABYRINTHECTOMY AND VESTIBULAR NEURECTOMY

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Unilateral vestibular injury evokes a characteristic pattern of acute disorganization of posture, locomotion, and eye movements. Following this acute stage, functional recovery occurs. In the present study, unilateral labyrinthectomy and vestibular neurectomy were performed in cats. The lateral vestibular nucleus (LVN) and vestibular nerve root entry zone on both sides of the brain stem were examined 24 hours, 3 days, and 8 weeks after operation by use of an immunochemical astrocyte marker, glial fibrillary acidic protein (GFAP). The results demonstrate extensive GFAP immunoreactivity within the ipsilateral nerve root following neurectomy, but not after labyrinthectomy. Prominent GFAP-immunoreactive astrocytic processes were detected in the LVN both ipsilateral and contralateral to neurectomy and labyrinthectomy. Within the ipsilateral LVN, the intensity of GFAP immunoreactivity was greater following neurectomy than after labyrinthectomy, but the pattern of GFAP reactivity remained similar. In the contralateral LVN, GFAP reactivity was noted exclusively in the dorsal-rostral region corresponding to the zone of cerebellar afferents to the LVN. The results of the present study suggest that reactive astroglia may play an important role in the mechanism that leads to vestibular compensation.

KEY WORDS — astrocytes, glial fibrillary acidic protein, immunoreactivity, labyrinthectomy, lateral vestibular nucleus, vestibular neurectomy.

INTRODUCTION

Following injury to the vestibular labyrinth or primary vestibular nerve, humans and other mammals display a characteristic vestibular syndrome consisting of spontaneous nystagmus, dynamic vestibulo-ocular reflex deficits, head and body twisting, and gait disturbance.[1] The recovery to near normal of these symptoms is referred to as vestibular compensation. The vestibular syndrome that follows acute vestibular injury is correlated with dysfunction and imbalance of neural activity within the paired vestibular nuclei.[2]

The primary vestibular neuron with its cell body in Scarpa's ganglion is the major source of excitatory neural input to the vestibular nuclei. The acute loss of the excitatory drive following vestibular neurectomy leaves neurons of the ipsilateral vestibular nucleus unresponsive to vestibular stimulation. Because inhibitory vestibular neurons that project across the midline to the contralateral vestibular nucleus are silenced also, neural activity within the contralateral nucleus almost doubles.[3] Moreover, increased neural activity of contralateral inhibitory neurons that project back to the ipsilateral deafferented vestibular nucleus results in even greater depression of activity in the deafferented nucleus. During the period of imbalanced neural activity, symptoms of the vestibular syndrome are maximal.[1]

Vestibular compensation proceeds as rapid rebalancing of neural activity occurs.[1-3] Neural activity within the deafferented vestibular nucleus reappears and increases, but never reaches preinjury levels. Neural activity within the contralateral vestibular nucleus is attenuated and gradually drops to levels close to but greater than preinjury levels. Although the physiologic characteristics of vestibular compensation have been well defined, the exact mechanism by which neural activity is regenerated in the ipsilateral nucleus and normalized in the contralateral nucleus is not known.

Most morphologic correlates of vestibular compensation either have been limited to an analysis of the ipsilateral nucleus or have noted degenerative changes occurring only in the vestibular nucleus ipsilateral to injury.[4-7] Mugnaini et al[4] studied the lateral vestibular nucleus (LVN) in cats following vestibular neurectomy or cerebellectomy. They showed that astrocytes react early in bouton modification and later in bouton shedding and degeneration. This response was identified only ipsilateral to injury, and no signs of synaptic plasticity were noted. Schwarz et al[5] noted the appearance of glycogen granules and microfilament hyperplasia within boutons both ipsilateral and contralateral to vestibular neurectomy in rats. An astrocytic reaction was noted, however, only in the ipsilateral vestibular nuclei. Korte and Friedrich[6] provided evidence of synaptic remodeling based on changes in vesicle morphology within the deafferented superior vestibular nucleus of the cat 5 to 6 days after vestibular neurectomy. No identification of astroglia

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was made, and only the ipsilateral nucleus was studied. Eight weeks and 1 year following vestibular neurectomy in the cat, Gacek et al[7] carried out an ultrastructural investigation of vestibulo-ocular neurons in the superior vestibular nucleus that were labeled retrogradely after horseradish peroxidase injection into the oculomotor nucleus. A reduction of synaptic profiles to 26% of normal was found at both times, implying no new synapse formation. Changes in synaptic vesicle morphology were noted in addition to an extensive astroglial reaction that apparently sealed off vacated postsynaptic sites. All of these responses were seen in the ipsilateral nucleus; no contralateral vestibular neurons were studied.

Since the dynamic changes that lead to balanced neural activity in the vestibular nuclei occur on both sides of the brain, the question raised by the present investigation was whether or not morphologic alterations could be detected not only in the ipsilateral vestibular centers, but also in the vestibular nuclei contralateral to injury. Glial fibrillary acidic protein (GFAP) immunoreactivity was used in the present study to detect the astroglial response in the LVN on both sides of the brain. In addition, an effort was made to identify differences in the astroglial response following labyrinthectomy and vestibular neurectomy, since it has been suggested that the vestibular nerve does not degenerate following labyrinthectomy.[8] The results of the present study suggest that astroglia play an important role in the mechanism that leads to vestibular compensation.

MATERIALS AND METHODS

Sixteen conditioned adult female cats (2.8 to 3.5 kg) were anesthetized with a mixture of ketamine (20 mg/kg) and Rompun (1 mg/kg) intramuscularly and prepared for aseptic operation. Labyrinthectomy was carried out on seven animals, while vestibular neurectomy was performed on seven additional animals. Two animals served as controls (one sham craniotomy, one unoperated).

Operative Procedures. For labyrinthectomy, the tympanic bulla was approached ventrally and opened to expose the round window and basal turn of the cochlea. Bone between the round and oval windows was removed, and the membranous labyrinth was excised with elevators, picks, and suction. Gelfoam then was packed into the vestibule, and the subcutaneous tissues and skin were closed in layers. In animals subjected to vestibular neurectomy, a labyrinthectomy was performed first. The medial wall of the vestibule and basal cochlea then was removed with use of a cutting bur to expose the internal auditory canal. The vestibular nerve, facial nerve, and cochlear nerve were identified, and a segment of the vestibular nerve containing Scarpa's ganglion was excised with microscissors. The resultant bony defect was packed with Gelfoam, and the wound was closed.

Postoperative Care. All animals were treated in accordance with the procedures outlined by the National Institutes of Health by the Department of Laboratory Animal Resources at Wayne State University. The animals were kept in separate cages at night, but were free to exercise and roam in a large room during the day. Normal diurnal light variation was maintained.

Tissue Preparation. Within each experimental group, the animals were assigned survival periods of 24 hours (two cats), 3 days (two cats), or 8 weeks (three cats). The sham-operation control animal was placed into a 3-day survival group. Following the assigned survival period, each animal was anesthetized deeply with pentobarbital (30 mg/kg) and transcardially perfused with 500 mL of normal saline in 0.1 *M* phosphate buffer (pH 7.4) followed by a 1,000-mL solution of 4% paraformaldehyde and 0.2% glutaraldehyde in 0.1 *M* phosphate buffer (pH 7.4). After perfusion the brain stem was removed and embedded into 7% agar. Fifty-micron Vibratome sections through the region of the LVN were cut and then reacted by use of the unlabeled antibody peroxidase-antiperoxidase immunochemical technique described by Sternberger[9] to detect GFAP in astrocytes.[10] Reacted sections were placed on slides and coverslipped with Aquamount.

RESULTS

Control Studies. The GFAP immunochemical reaction was identical in both the unoperated and sham-operated control animals. Immunoreactivity to GFAP was detected at the pia-glial limiting membrane as well as around the lumen of blood vessels (Fig 1A). Generally, little GFAP reactivity was noted within the vestibular nerve root or within the neuropil of the LVN (Fig 1A). High-power magnification revealed very little GFAP reaction product in association with the surface of neuronal cell bodies of the LVN (Fig 1B).

Chronic Vestibular Neurectomy. Since vestibular compensation is for the most part complete by 8 weeks postinjury in the cat,[7] we elected to examine first the GFAP astrocytic reaction at this time. Eight weeks following vestibular neurectomy, a dense glial scar was noted within the vestibular nerve root (Fig 2A,B). Higher magnification of the nerve root (Fig 2B) revealed a heavy deposition of reaction product that was arranged mostly along the longitudinal axis of the nerve. Furthermore, the transected nerve was characterized by cystlike inclusions that always were surrounded by reaction product.

In addition to the glial reaction detected within the injured nerve root, a prominent glial response was seen in the neuropil of the ipsilateral LVN (Fig

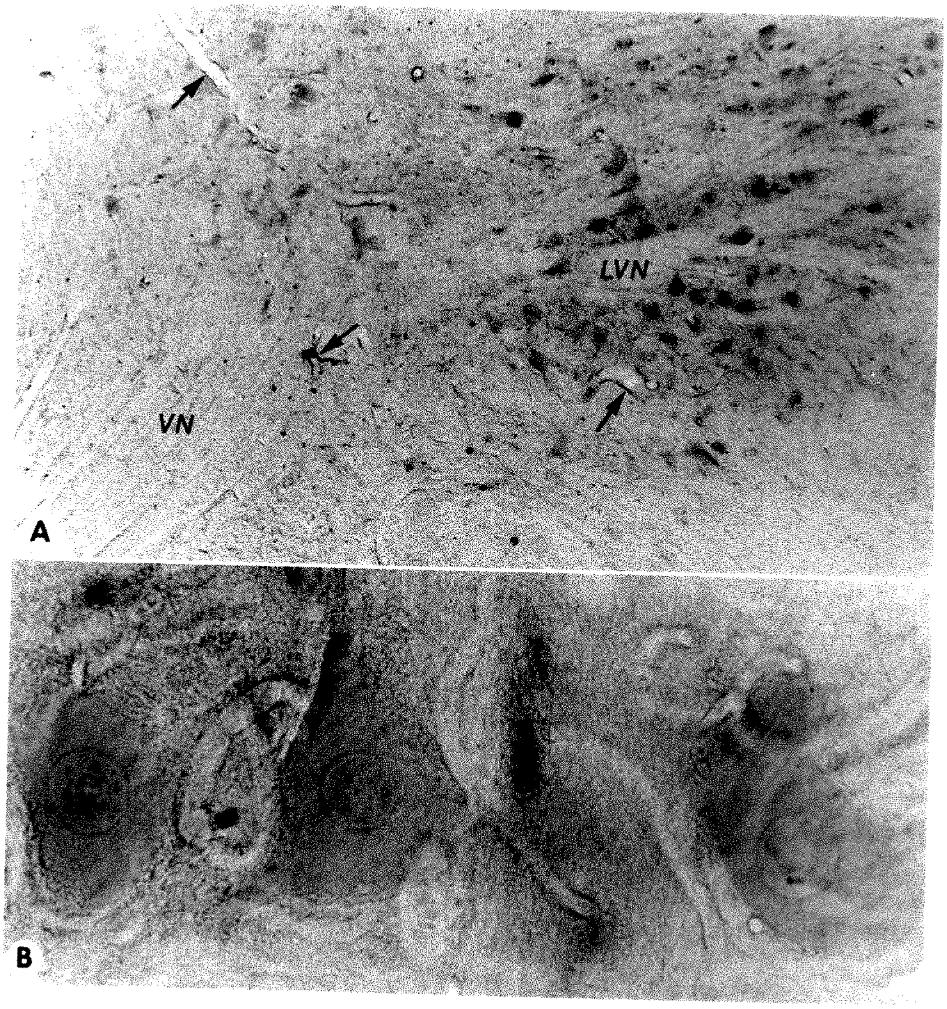

Fig 1. Glial fibrillary acidic protein (GFAP)-stained sections from control animal. A) Photomicrograph showing orientation of vestibular nerve root (VN) and lateral vestibular nucleus (LVN) (original x64). Arrows — GFAP-stained glial processes in association with blood vessels. Note nonspecific IgG reaction producing some background staining in neurons and their processes. This nonspecific staining is distinguished readily from GFAP reaction product seen in reactive astrocytes. B) Photomicrograph showing neurons of LVN (original x630). Note that GFAP reactivity is not seen on surface of these cells in normal animal.

2A-D). This reaction was characterized by the presence of numerous thick glial processes in the neuropil (Fig 2C), as well as a conspicuous glial response that surrounded the neuronal cell bodies (Fig 2C,D).

The astroglial response was not restricted to the injured vestibular nerve root and the ipsilateral LVN. Increased GFAP immunoreactivity also was detected within the contralateral LVN (Fig 2E,G,H). The glial response noted in the contralateral LVN was most prominent in the dorsal-rostral regions of the nucleus (Fig 2E) and absent in the ventral-caudal area (Fig 2E). Although the pattern of GFAP reactivity within the contralateral nucleus is different from the dense reactivity seen in all areas of the ipsilateral LVN (compare Fig 2A and 2E), at higher magnification the characteristics of the response are similar to the ipsilateral reaction, with prominent glial processes detected in the neuropil (Fig 2G) and surrounding neuronal cell bodies (Fig 2G,H).

In contrast to the dense glial scar seen in the injured vestibular nerve root, minimal GFAP reactivity was seen in the unaffected, contralateral nerve root (compare Fig 2B and 2F). The GFAP reactivity noted in the contralateral nerve root was no different from the reactivity seen in the nerve roots of the control animals.

Chronic Labyrinthectomy. Eight weeks following labyrinthectomy, glial reactivity was noted in the ipsilateral nerve root and LVN (Fig 3A,B). The glial response in the ipsilateral nerve root was greater than that seen in controls, but far less intense than the reaction seen in the ipsilateral nerve root following neurectomy (compare Figs 3A and 2B). Similarly, the glial response seen in the ipsilateral LVN also was greater than that in controls, but not as intense as the reaction in the ipsilateral LVN following neurectomy (compare Figs 3B and 2C). In spite of the differences in intensity noted in the ipsilateral nerve root and LVN following labyrinthectomy and neurectomy, the general pattern of reactivity was the same following the two procedures. A few longitudinally oriented glial processes were seen in the vestibular nerve root, while prominent glial processes were noted both in the neuropil and in surrounding LVN neurons.

The glial reactivity seen in the vestibular nerve root contralateral to the side of labyrinthectomy (Fig 3C) was similar to the reactivity observed in

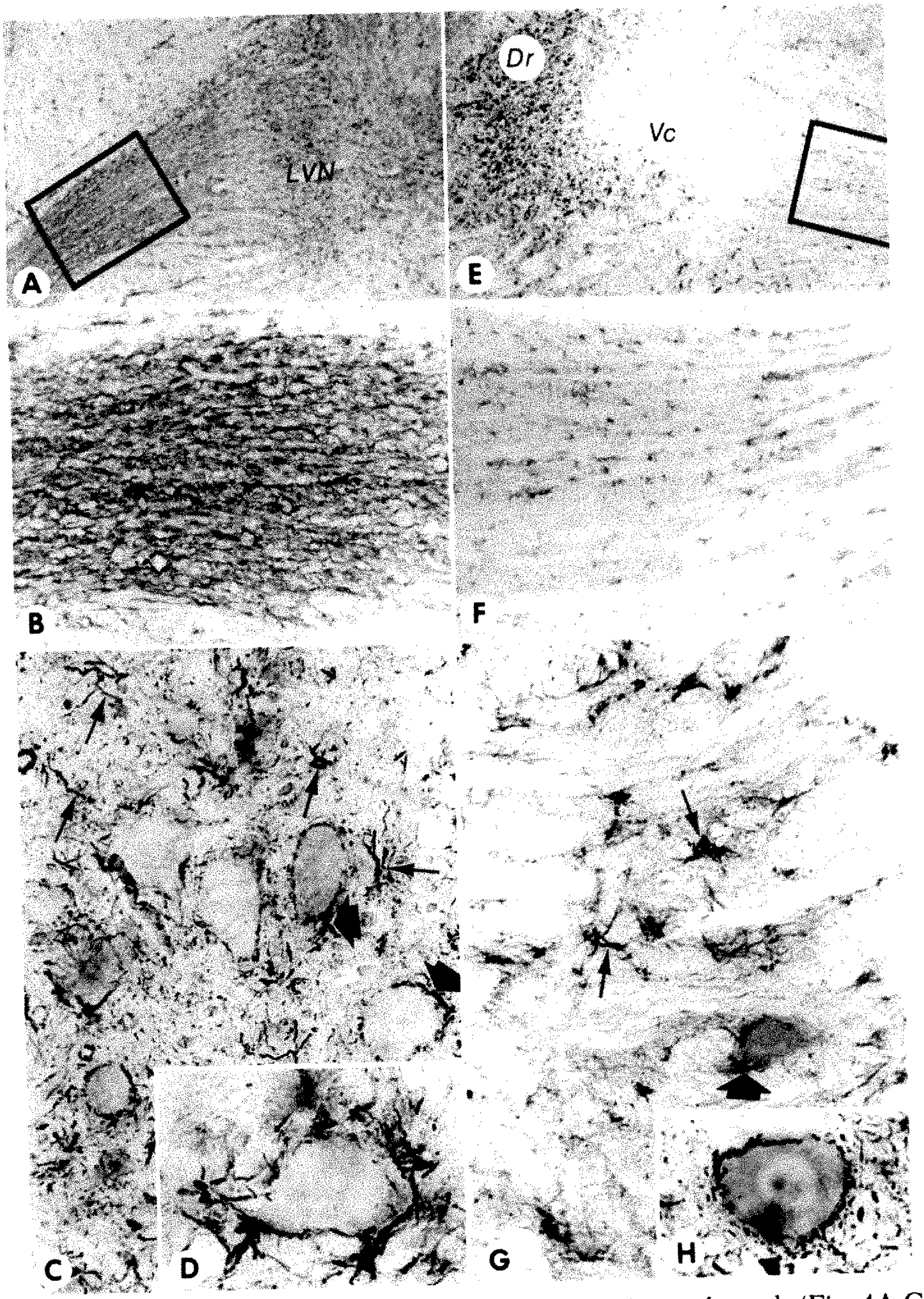

Fig 2. Ipsilateral and contralateral glial fibrillary acidic protein (GFAP) immunoreactivity 8 weeks following vestibular neurectomy. Low-magnification views of nerve root and lateral vestibular nucleus (LVN) in A and E were rotated so that dorsal-rostral zone appears medial in photomicrographs. A) Micrograph showing GFAP response in injured nerve root and ipsilateral LVN (original x27). Area within rectangle is enlarged in B. B) High-magnification view of reactive glial response in injured nerve root (original x90). Note reactive astroglial processes that run along longitudinal axis of nerve, as well as cyst-like inclusions in nerve. C) GFAP immunoreactivity in ipsilateral LVN (original x240). Small arrows — prominent reactive glial processes in neuropil, large arrows — immunoreactivity that surrounds individual neurons within nucleus. D) High-magnification view of single neuron in ipsilateral LVN 8 weeks after neurectomy (original x1,200). Entire surface of cell in this section is covered by prominent reactive astroglial processes. E) Micrograph showing GFAP response in contralateral nerve root and LVN (original x27). Astrogliosis is prominent only in dorsal-rostral (Dr) zone of contralateral LVN. Ventral-caudal (Vc) zone is relatively free of reactive glial processes. Area of contralateral nerve root within rectangle is enlarged in F. F) High-magnification view of contralateral nerve root showing that glial process reactivity is minimal (original x90). This response is indistinguishable from that of control animals. G) Astroglial response of contralateral LVN (original x240). Small arrows — glial processes in neuropil, large arrow — reactivity surrounding individual cell. H) High-magnification photomicrograph of single neuron in contralateral LVN 8 weeks following neurectomy (original x435). As in D, entire surface of this cell is covered by reactive astroglial processes.

the nerve root contralateral to neurectomy (Fig 2F) as well as in the control nerve roots. In the LVN contralateral to labyrinthectomy (Fig 3D), the observed glial response was indistinguishable from the LVN glial response ipsilateral to labyrinthectomy (Fig 3B). The regional differences in glial reactivity observed in the contralateral LVN following neurectomy were not detected as easily in the LVN contralateral to labyrinthectomy.

Acute Studies. In an attempt to correlate the early phases of vestibular compensation with the onset of morphologic changes in the vestibular centers, animals subjected to vestibular neurectomy and labyrinthectomy were analyzed at both 3 days and 24 hours after operation. Three days following neurectomy and labyrinthectomy, the astroglial response was already well developed in both the ipsilateral (Fig 4A,C) and contralateral (Fig 4B,D) LVNs. The induction of the glial response in the LVN following either procedure was very rapid. Detection of the glial response bilaterally within the LVN following neurectomy (Fig 4E,F) or labyrinthectomy was made 24 hours after operation, which was the earliest survival period examined. Glial reactivity within the vestibular nerve roots, however, was not detected this early after operation. This suggests the possibility that early metabolic or electric changes occurring in the LVN result in glial reactions prior to the glial reaction induced by degeneration of the nerve.

DISCUSSION

The present study demonstrates an increase in astroglial GFAP immunoreactivity in both the ipsi-

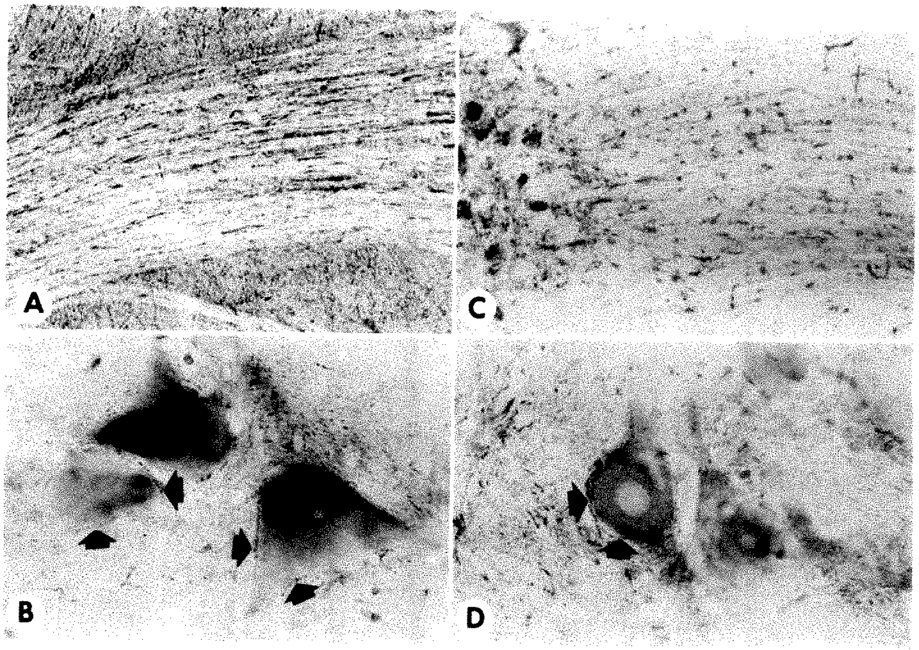

Fig 3. Ipsilateral and contralateral glial fibrillary acidic protein (GFAP) immunoreactivity 8 weeks following labyrinthectomy. A) Vestibular nerve root showing degree of GFAP immunoreactivity ipsilateral to labyrinthectomy (original x74). B) High-magnification view of three neurons in lateral vestibular nucleus (LVN) ipsilateral to labyrinthectomy (original x260). Arrows — GFAP immunoreactivity surrounding cells. C) GFAP immunoreactivity in vestibular nerve root contralateral to labyrinthectomy is minimal (original x140). D) High-magnification view of neurons in LVN contralateral to labyrinthectomy (original x260). Arrows — GFAP immunoreactivity surrounding cells.

lateral and contralateral LVNs in response to unilateral labyrinthectomy or vestibular neurectomy. The heavy GFAP reaction product seen within the injured vestibular nerve root following neurectomy is most likely due to the degeneration of primary vestibular afferent axons. By comparison, after labyrinthectomy only minimal GFAP immunoreactivity was present in the vestibular nerve root, suggesting that extensive axonal degeneration does not occur following labyrinthectomy. Examination of silver-impregnated sections confirmed complete axonal degeneration in the nerve root following neurectomy, while little axonal degeneration was noted in the nerve root following labyrinthectomy (unpublished data). Survival of the vestibular nerve following labyrinthectomy was first hypothesized by Dohlman.[11] It is not known presently if the survival of the primary afferent vestibular nerve affects vestibular compensation. However, in support of this notion, Jensen[8] has demonstrated residual spontaneous neural discharges within the vestibular ganglion of the guinea pig following labyrinthectomy and suggested that this residual neural activity may be propagated over surviving primary vestibular axons to promote vestibular compensation.

Unlike the dense glial scar seen in the vestibular nerve root following neurectomy, the GFAP immunoreactivity observed within the LVN ipsilateral to neurectomy or labyrinthectomy forms its own distinct pattern. Specifically, prominent GFAP immunoreactive astroglial processes were observed surrounding neuronal cell bodies, as well as being interspersed in the neuropil. The observed GFAP reactivity was distributed evenly throughout both the termination region of the primary vestibular afferents (ventral-caudal zone) and the region of cerebellar inputs (dorsal-rostral zone). The only difference in the response between labyrinthectomy and neurectomy is that the GFAP reactivity is more intense following neurectomy. Thus, the GFAP reactivity in the ipsilateral LVN is most likely due both to degenerative changes involving the removal of the primary vestibular afferent terminals[7] and to metabolic changes occurring in neurons of the nucleus.

Graeber and Kreutzberg[12] demonstrated a similar pattern of GFAP reactivity in the facial nucleus during the metabolic changes occurring in the facial motor neurons following axotomy and subsequent regeneration of the facial nerve. They suggested that GFAP-reactive astrocytes play an important role during neuronal recovery following injury. This speculation is tempting in view of the growing evidence that astrocytes are capable of specialized functions such as regulation of synaptic density,[13] high sodium-potassium ATPase activity,[14] and the uptake and synthesis of neurotransmitters.[15]

Within the contralateral LVN, the GFAP immunoreactivity was localized in regions that receive primarily cerebellar afferents. The region of the contralateral LVN that receives the primary vestibular afferents was free of GFAP reactivity. The pattern of GFAP reactivity in the contralateral LVN is consistent with the fact that there are no known primary vestibular afferents that project to the contralateral LVN.[16] Thus, the GFAP reactivity within astrocytes in the contralateral LVN cannot be due to a direct degenerative reaction of the primary vestibular nerve. Rather, the contralateral astroglial reaction is most likely due to electric and metabolic changes that occur in the contralateral vestibular nuclei during vestibular compensation.[3]

It is not known what stimulates the astroglia to react in the contralateral LVN. However, there is

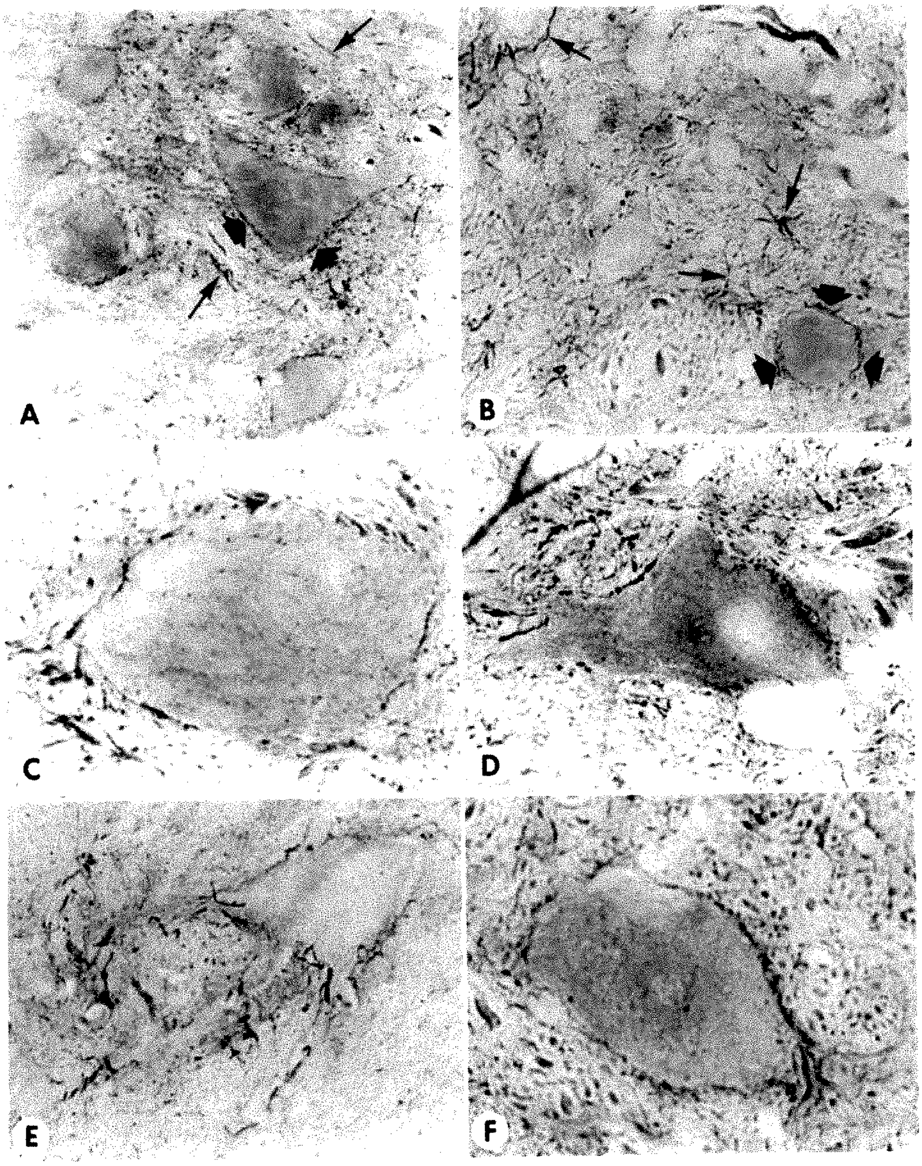

Fig 4. Glial fibrillary acidic protein (GFAP)-stained sections through ipsilateral and contralateral lateral vestibular nucleus (LVN) following acute neurectomy and labyrinthectomy. A) Photomicrograph of ipsilateral LVN 3 days after neurectomy (original x235). Small arrows — prominent glial processes in neuropil, large arrows — GFAP immunoreactivity on surface of neuron. B) Photomicrograph of contralateral LVN 3 days after neurectomy (original x490). Small arrows — glial processes in neuropil, large arrows — glial processes surrounding individual cells. C) High-magnification view of neuron in ipsilateral LVN 3 days after labyrinthectomy (original x800). Note glial processes that almost entirely envelop cell. D) High-magnification view of neuron in contralateral LVN 3 days after labyrinthectomy (original x900). Immunoreactivity is seen both in neuropil and surrounding cell. E) Neuron of ipsilateral LVN 24 hours after neurectomy (original x480). Extensive GFAP is seen around borders of cell, in neuropil, and on adjacent blood vessels. F) Single neuron in contralateral LVN 24 hours following labyrinthectomy (original x710). Immunoreactivity surrounds most of perimeter of this neuron.

evidence in the literature that is suggestive of two possible mechanisms. It is known that astroglia have the ability to absorb extracellular potassium. Moreover, an actively depolarizing neuron releases potassium into the extracellular space.[17] Since neurons of the contralateral LVN are hyperactive acutely following peripheral vestibular injury,[3] they are most likely releasing large quantities of potassium into the extracellular space. It is therefore possible that thin astroglial processes, which have been shown to surround individual neuronal profiles within the LVN,[18] may hypertrophy in response to elevated extracellular potassium's being released from the hyperactive vestibular neurons. The morphologic consequence of this response is the detection of GFAP immunoreactivity surrounding neurons in the LVN. Furthermore, since astroglia hyperpolarize when they absorb excess extracellular potassium,[17] it is possible that glial hyperpolarization may help to stabilize adjacent hyperexcitable vestibular neurons.

Another explanation for the enhanced GFAP immunoreactivity observed within the contralateral LVN may be related to alterations of cerebellar afferents that terminate in the same region of the LVN. Thompson et al[19] demonstrated a marked reduction of γ-aminobutyric acid (GABA) immunoreactivity within the same regions of the LVN in which enhanced GFAP immunoreactivity was detected in the present study over the same time period following labyrinthectomy. The GABA originates from cerebellar Purkinje cell axons[20] that project to the dorsal-rostral region of the LVN.[16] The decrease of the inhibitory neurotransmitter GABA within synaptic terminals correlates with the enhanced excitability of vestibular neurons following contralateral peripheral vestibular injury. There is evidence that astroglia hypertrophy and insinuate their processes between nonfunctioning synaptic terminals and postsynaptic targets.[21] Thus, the enhanced GFAP immunoreactivity seen in the contralateral LVN may be due to the removal of nonfunctional synaptic terminals, an elevation of extracellular potassium, or both.

SUMMARY

The present study has shown that during the recovery from injury to the peripheral vestibular system, astroglia become GFAP-immunoreactive within the LVN on both sides of the brain. The GFAP-immunoreactive astroglia that are ipsilateral to labyrinthectomy or vestibular neurectomy may have been stimulated to produce GFAP by the degeneration products from injured primary vestibular axons, or by degenerating synaptic terminals. However, since dynamic metabolic and electric changes occur in the LVN on both sides of the brain during vestibular compensation, the GFAP-immunoreactive astroglia within the contralateral LVN as well as the LVN ipsilateral to injury may have been stimulated by the physiologic alterations occurring in the LVN during vestibular compensation. The results of the study suggest that in addition to the traditional role of astrocyte phagocytosis during degenerative responses within the CNS, other astroglial phenomena are involved in presynaptic and postsynaptic reorganization following vestibular injury.

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FATIGUE RESISTANCE OF CANINE VOCAL FOLD MUSCLE

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The objective of the experiment was to provide data from dogs, the best nonprimate model for the contractile properties of laryngeal muscles, on the fatigue characteristics of vocal fold muscle. Isometric muscle force was recorded from a transducer attached to the section of the thyroid cartilage on which the muscle inserted. Twitch contractions were recorded during supramaximal indirect electrical stimulation by DC pulses for at least 30 minutes. At 5 pulses per second (p/s), potentiation was observed in all records, peaking at an average of 7.5 minutes after stimulation onset. At 10 p/s, the peak of the potentiated average trace was earlier. One third of these records did not show potentiation. Where moderate or large potentiation was observed, the peak twitch tension declined and reached an asymptote above the initial tension, while when potentiation was small or absent, the final force was smaller than initially. Canine vocal fold muscle was observed to be fatigue-resistant, but in phonation other factors may produce fatigue.

KEY WORDS — fatigue, larynx, thyroarytenoid muscle, vocalis muscle.

INTRODUCTION

Much attention has been devoted to the subject of vocal fatigue, a term that sounds as if it belongs to physiology, although published studies usually have rested on an acoustic basis. Vocal fatigue is probably multifactorial in causation, but the present study will be restricted to consideration of muscle fatigue in the larynx. At a different extreme involving life support functions of the larynx, Hinrichsen and Dulhunty[1] have found that rat posterior cricoarytenoid and cricothyroid muscles are susceptible to fatigue, and suggested that this may be true of the human posterior cricoarytenoid muscle also, with resulting susceptibility to upper airway obstruction. In fact, very limited information is available about the fatigue properties of the structures of the upper airway. Recently, inspiratory muscle fatigue has been the subject of a number of studies,[2] but studies of the larynx are limited and of uncertain relevance. In a study of the histochemical properties of cat laryngeal muscles, Edstrom et al[3] published evidence that the cat cricothyroid muscle was quite fatigue resistant to stimulation at 5 and 10 pulses per second (p/s), and indicated that the thyroarytenoid and lateral cricoarytenoid muscles behaved similarly. They found that at both 5 and 10 p/s, cricothyroid muscle showed much less fatigue than did the anterior tibialis, which is composed of more fatigable fibers. With stimulation at 5 p/s, at 17 minutes the cricothyroid muscle dropped to 88% of its initial twitch tension, while at 10 p/s, it had fallen to about 84% at almost 10 minutes of stimulation, indicating a faster progress of fatigue at the higher stimulation rate. A small potentiation (rise in tension), peaking at about 6 minutes, is observable in their data at 5 p/s, but not at 10 p/s.

Zealear[4] has examined the fatigue characteristics of cat thyroarytenoid single motor units at 10 p/s, as well as at higher pulse rates. At 10 p/s, he found that fast motor units showed initial potentiation, and when stimulated for as long as an hour maintained twitch tensions above their initial level but below the peak potentiated level. Fast red motor units were just as fatigue-resistant as slow units. The divergence of these findings from those of Hinrichsen and Dulhunty[1] raises the question of whether either model provides an appropriate basis for extrapolation to humans.

Hast[5] has found that canine laryngeal muscles are similar in their contractile properties to those of primates, more similar than those of cats. However, no study has focussed on the fatigue characteristics of canine laryngeal muscles. Studies on a histochemical basis have indicated that laryngeal muscles of larger mammals contain various proportions of type 1 fibers, which are slow-contracting and fatigue-resistant, with a strong oxidative metabolism, and type 2A fibers, which are fast-contracting, with a mixed oxidative-glycolytic metabolism; very small quantities of other types of fibers have been found.[3,4,6,7] Type 2A fibers are more fatigue-resistant than the fast, fatigable type 2B fibers, which have a mainly glycolytic metabolism, but in limb muscles type 2A fibers are not as fatigue-resistant as type 1 fibers.[8] The proportions of different types of thyroarytenoid muscle fibers in the cat, the dog, and various primates are indicated in the Table.[3,4,6,7,9-12] In the cat and dog there are found some subtypes of fibers within the type 2A.[3,6]

From the Table it appears that feline, canine, and human laryngeal muscles contain respectively

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From the Department of Otolaryngology, School of Medicine, University of Southern California, Los Angeles. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Southern California.

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PROPORTIONS OF MUSCLE FIBER TYPES IN THYROARYTENOID MUSCLE

Species	*Studies*	*Type 1*	*Type 2*
Cat	Edstrom et al[3] Zealear[4] Mascarello and Veggetti[6]	10%	90%
Dog	Mascarello and Veggetti[6]	20%	80%
Rhesus	Sahgal and Hast [7]	19%	81%
Human	Rosenfield et al[9] Teig et al[10] Sadeh et al[11] Bendiksen et al[12]	42%*	58%*

*Means across studies weighted by number of subjects in each study.

increasing amounts of fibers with a predominantly oxidative metabolism.[9-11] Thus, laryngeal muscles may increase in terms of their resistance to fatigue in relation to the size, weight, and configuration of the respiratory structures they control, and perhaps decrease in contraction speed, although only indirect evidence is available for the speed of human laryngeal muscles.

The present study was undertaken to examine the response of canine vocal fold muscles to prolonged activation, as the best available model for those of humans. Since the mechanical effects of vocalis and thyroarytenoid muscles cannot be distinguished by the measurement procedure used, they are referred to collectively as vocal fold muscles, although Kersing[13] has shown that there are minor histochemical differences between the two subdivisions in the dog. His findings also emphasize the individual variability of proportions of muscle fibers of different types.

Four of the animals studied were available because in other research the opposite vocal fold had been subjected to reinnervation by anastomosis to the ansa cervicalis. This was not a matter of design, but one of availability of material. Since below the lower motor neuron there are no crossed motor connections of peripheral nerves innervating the canine thyroarytenoid muscle, reactive changes in motoneurons of the proximal section of the severed recurrent nerve should not affect contralateral neuromuscular function. However, a clinical question arises as to the effect of surgical procedures on the fatigue resistance of laryngeal muscles. Since there is evidence that fatigue resistance of skeletal muscles is not altered by reinnervation,[14] this question concerns not so much the reinnervated muscle as the functional opposite muscle, which might have become more fatigue-resistant if its activity was increased to compensate for the absent or uncoordinated activity of the operated muscle.[15] Consequently, this material is usable only if the response of the muscles of these animals to continued activation is similar to that of the three unoperated animals.

Peripheral fatigue in indirectly activated muscle may be measured experimentally as decline in isometric tension. It can result from at least four different causes: 1) failure of neurotransmission at the myoneural junction, 2) failure of propagation of the muscle action potential, 3) failure of excitation-contraction coupling, and 4) failure of the contractile mechanism.[8] Each of these causes may be analyzed into various subcomponents. On an experimental level an important distinction in terms of the stimulation rate is drawn between high-frequency fatigue and low-frequency fatigue, which affect these successive stages differently. There is incomplete agreement as to the physiologic basis of these effects, but fatigue at high stimulus pulse rates is partly attributable to effects at the motor end plate. For this reason the present study has been limited to consideration of the response to stimulation at low pulse rates. Briefly it should be added that for mathematical reasons this rate terminology is preferable to the customary frequency terminology, since the Fourier transforms of the corresponding impulse trains differ not in the high or low frequency location of spectral energy, but in the density and amplitude of the impulses that compose them.

METHODS

In general the procedures followed those originated in 1929 by Bruin,[16] used by several intervening investigators, and more recently elaborated by Hast[5] in studies on the contractile properties o canine vocal fold muscles. The animals were anesthetized and supine on the operating table. The position of the head on the operating table wa fixed. The larynx was exposed by an incision extending from the hyoid bone to above the sternum A tracheotomy was performed to preserve a free ai passage and detach the upper section of the trachea and larynx from the effects of tracheal pull during respiration. The recurrent laryngeal nerve was dissected free from the surrounding tissues before it entry into the larynx on one side. A window was cu in the thyroid cartilage, around the anterior insertion of the vocal fold muscles, so that the anterio attachment of the vocal cord was freed. Thus the piece of cartilage was able to move freely in the anterior-posterior direction. The posterior attachment of the vocal fold muscles was immobilized by piercing the arytenoid cartilage in adducted position with a long needle, which was fixed in the cricoid cartilage. The cricoid cartilage was fixed by a clamp attached to an external stand. Thus, although the recurrent nerve stimulation presumably activated all of the ipsilateral laryngeal muscles except the cricothyroid, there could be no relative motion of the arytenoid and cricoid cartilages, so tha activation of the other muscles could not contaminate isometric measurements of vocal fold muscle contraction.

The section of the thyroid cartilage that forms the anterior boundary of the vocal fold muscles was attached by a Tevdek 2-0 polyester suture to an iso

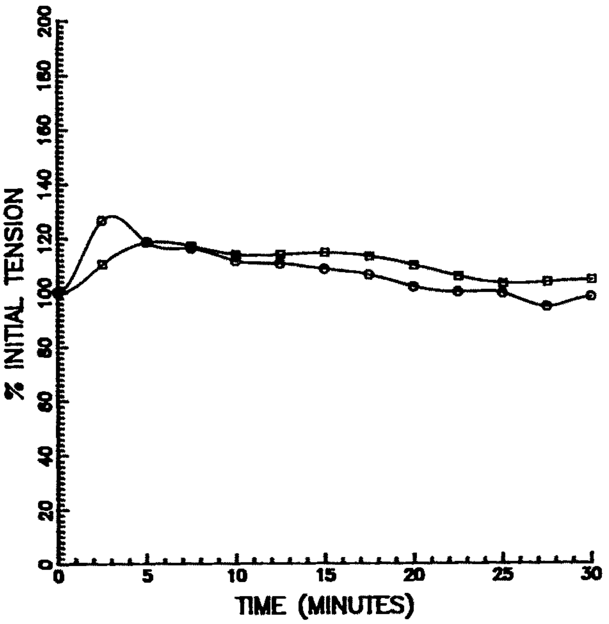

Fig 1. Smoothed line connecting squares separated by 2.5 minutes indicates mean record for three dogs on which no reinnervation procedure was performed. Smoothed line connecting circles indicates mean record for four dogs on which reinnervation procedure had been performed on opposite vocal fold muscle.

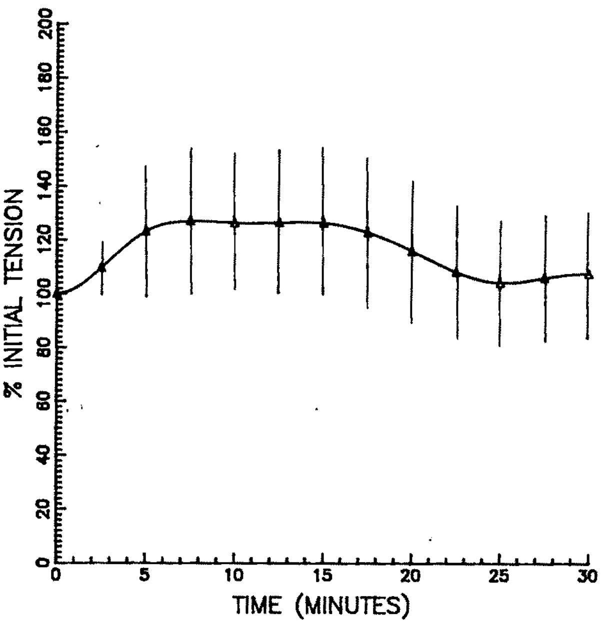

Fig 2. Smoothed line connecting triangles separated by 2.5 minutes indicates mean of all records for three dogs in which vocal fold muscles were activated by electric stimulation at 5 pulses per second (p/s). Vertical lines indicate standard deviation across animals.

metric force transducer that produced an electrical output proportional to the force exerted by the muscle in isometric contraction. This signal was calibrated by hanging known weights from the force transducer. The signal from the transducer was fed to the analog-to-digital converter of a computer.

The recurrent nerve was stimulated by an electrode hooked around it; DC pulses with a duration of 0.2 ms were used, slightly longer than the 0.1 ms recommended by Kimura[17] as long enough to fully activate a healthy peripheral nerve given an appropriate stimulus level. In different experiments the nerve was stimulated continuously at 5, 10, or 20 p/s. Slow rates of stimulation were used for two reasons: first, so that the results would be comparable to those of Edstrom et al[3] and Zealear[4] for cat thyroarytenoid muscle, and second, to avoid impairment of neuromuscular transmission at the motor end plate, which can occur above slow stimulus rates.[2] This is not meant to imply that faster response rates are not to be taken into account in further experimentation. Faaborg-Andersen,[18] working in Buchthal's laboratory, found that single motor units of human vocalis muscle fired at rates of about 10 to 40 times/s in phonation, although the mode in his figures appears to be about 25 times/s. Sawashima[19] found a maximum firing rate of 20/s in human vocal fold muscle. Knutsson et al[20] found the same range in human vocal fold muscle in nonspeech tasks as had Faaborg-Andersen. At the high end, Zealear[4] found bursts of firing at 350 to 450 discharges/s in fast motor units of cat thyroarytenoid muscle. Thus the stimulation rate used overlaps the low side of a realistic firing range for motor units of human vocal fold muscle.

RESULTS

We shall report data from seven animals, extending for 30 minutes after the onset of stimulation. It should be noted that in four cases the stimulation was prolonged for about an hour, but the level of muscle force showed little change after the first 30 minutes. Since digital storage was limited, data were recorded in bursts of about five to ten twitches at points in time separated by a mean of about 4.6 minutes. The force of isometric twitch contraction was measured as the rise from the level of passive force prior to the onset of contraction. The isometric force levels of all twitches during each burst were averaged. Since the absolute levels of initial force differed across animals, data were normalized in terms of percent of the initial contractile force, as in the study of Edstrom et al.[3] A cubic spline interpolation[21] between the resulting points was used to permit the construction of an average time course of fatigue across all animals in a given condition. These plots provide interpolated records of the peak tension of isometric twitches averaged across animals.

The first question that must be addressed is whether the operation on the opposite side of the larynx had produced any observable effects on the fatigue resistance of the muscles studied. For this purpose we lump all conditions together in Fig 1, which contrasts the averaged record for the un-

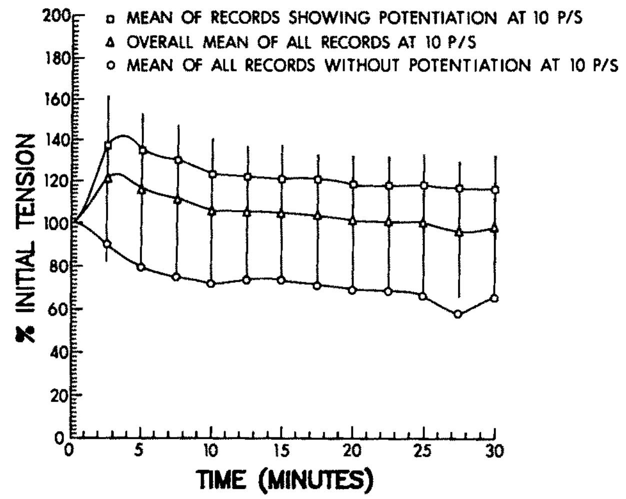

Fig 3. Smoothed lines indicate mean for records at 10 p/s. Vertical lines indicate standard deviation overall.

operated animals to the averaged record for those subjected to reinnervation on the opposite side. The difference in the location of the peak is accounted for by the fact that three of the operated animals were used in the study of the response to stimulation at 10 p/s as discussed below. The fact that the unoperated animals showed slightly greater resistance to prolonged stimulation reflects the fact that the operated group included three animals with little or no potentiation, as well as one with considerable potentiation. Potentiation was found in every unoperated animal, although in one case it was found at 5 p/s but not at 10 p/s. Since the general pattern of the response to prolonged muscle activation was the same in both groups of animals, they are treated together in the following discussion. It is possible that differences between the two groups could appear in a more extensive project than the present pilot study.

The response to stimulation at 5 p/s was studied in three animals (Fig 2). In this Figure and in Fig 3 the variability of the data is indicated by the plotting of 1 SD above and below the mean at intervals of 2.5 minutes. A slow rise in tension or potentiation was observed that in the averaged trace peaked at 7.5 minutes (in individual cases at 2.5 minutes, 7.5 minutes, and 15 minutes), after which the twitch contraction declined in force to a level that in every record was 20% to 30% below the peak reached during potentiation, leveling off to a value slightly above the initial force level by 22.5 to 25 minutes after the onset of stimulation.

The response to stimulation at 10 p/s (Fig 3) was studied in five animals, with two records made from one animal. Figure 3 provides three traces: a central one indicating the mean across all animals and records, an upper record showing the mean of data that included potentiation (four records from three animals), and a lower record indicating the mean of data that did not indicate potentiation (two animals). In the animal that was stimulated in

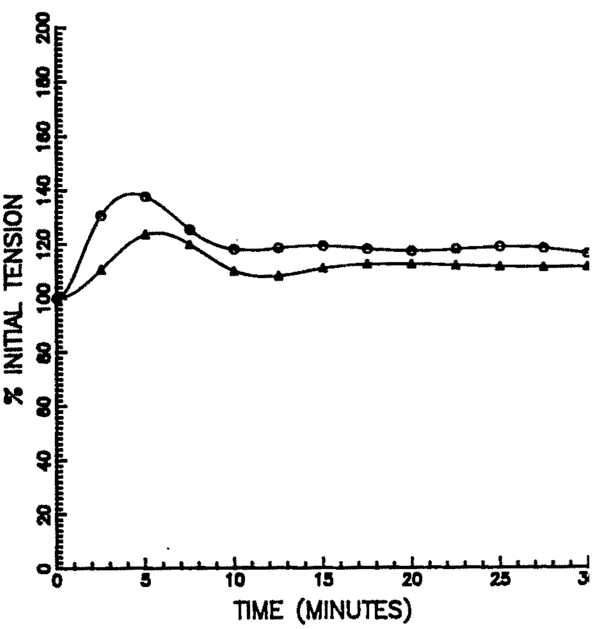

Fig 4. Line connecting triangles indicates response to prolonged activation at 10 p/s in first course of stimulation. Line connecting circles indicates response to second course of stimulation at same rate after 9 minutes of rest.

two series at the same rate (Fig 4), the overall tim course of the response agreed well, and the absolut levels of the eventual asymptote of peak twitch ter sion differed by only 3% in the two series. In ger eral, two different patterns of response were ob served at this rate of stimulation, since in two of th animals, no potentiation was observed, while i three of them various amounts of potentiation wer observed. In one case, no potentiation was observe at 10 p/s in an animal in which a potentiation c 40% had been observed previously at 5 p/s. In a cases in which there was a moderate or large poter tiation, the asymptote of force was above the initi level, while if the potentiation was small or absen the decline of force extended to between 50% an 90% of the initial level. It may be observed that th overall mean record for 10 p/s reaches its peak a just over 3 minutes, slightly under half of the tim lag required for the mean record for 5 p/s to reac its peak tension.

Only in one case was a muscle stimulated at 2 p/s, because of concern that this rate might er croach on a region in which the phenomena ob served would reflect impairment of neuromuscula transmission as well as muscle fatigue. The dat show an initial rapid decline of the force output c the muscle, rather than the potentiation observe during stimulation at slower rates, so this concer may have been justified. After this initial perioc the fatigue proceeded at a somewhat faster rat than at lower stimulation rates, and then reache an asymptote in the vicinity of 60% of the initi value.

DISCUSSION

The characteristic response of the vocalis musc to prolonged twitch activation at low rates observed in the present study may be described in terms of the phenomenon labelled "positive staircase" (in German "Treppe") in both cardiac muscle and normal skeletal muscle of both lower mammals and humans by Desmedt et al,[22] Slomic et al,[23] and others. In contrast to neuromuscular potentiation, this effect is thought to result from post-motor end plate factors, particularly the dynamics of the release and uptake of calcium ions in excitation-contraction coupling. For instance, in normal human adductor pollicis muscle, there is an increase ranging from 15% to 50% (mean, 25%) of the initial twitch tension during the first few minutes of continued stimulation at a slow rate, and then a decline.[22] In the data of Slomic et al,[23] as in ours, the increase could be as great as about 100%. Slomic et al found that this increase was the result of the number of stimuli applied rather than of the rate of stimulation; this finding is consistent with ours that a doubling of stimulation rate caused the peak twitch tension to be reached about twice as quickly at 10 p/s as at 5 p/s. The longer duration of the potentiation in the 5 p/s data is in principle consistent with this rule, although determination of the precise length of the potentiation is not clear in detail. What needs explanation is the finding that in some recordings, all at higher rates of stimulation, no staircase was observed. One factor is that the staircase phenomenon in muscle decreases both below 1 p/s and above 3 p/s,[22] ie, it is characteristic of a certain narrow slow band of stimulus rates, although it is possible that in the very fast vocal fold muscles this band is shifted upward. This would agree with the findings of Edstrom et al[3] for cat cricothyroid muscle, in which potentiation was observed at 5 p/s but not at 10 p/s. Another relevant factor may be that as stimulation rate increased, the anesthetic used may have affected the function of the neuromuscular junction. Although pentobarbital sodium was used in the present study for the sake of consistency with the preceding literature, in subsequent studies it should be compared with other anesthetics in the present application.

Since only one dog was studied with stimulation at 20 p/s, further research will be necessary to determine whether this pattern is characteristic. The fatigue pattern observed was comparable to that found by Edstrom et al[3] in the slower cat cricothyroid muscle at 10 p/s. It may well be that in the fast canine vocalis muscle we simply see a component of muscle fatigue at 20 p/s that in the slower cat cricothyroid muscle is seen at 10 p/s. Elucidation of this parallelism requires further study of the response to higher rates of stimulation, and resolution of the different components of laryngeal muscle fatigue.

We have not attempted to untangle the separate components of skeletal muscle fatigue in this study. Future studies should employ electromyography to assist in this. However, it should be noted that not all muscle fatigue processes can be expected to function in the same manner in our preparation as in humans. In particular, a number of researchers have pointed out the frequent presence of more than one motor end plate on a given laryngeal muscle fiber in various species, in contrast to the results of the extensive study of human biopsy material by Coers and Woolf,[24] who found more than one motor end plate on no more than 2.3% of the skeletal muscle fibers they studied. Bendiksen et al[12] found that in human thyroarytenoid muscle, 67% of the type 1 fibers had more than one motor end plate, while 28% of the type 2 fibers were innervated multiply. Clearly, one must distinguish between cases of polyneuronal innervation, in which more than one motor neuron sends axons to a given muscle fiber, as has been shown by Hunt and Kuffler[25] to occur in the cricothyroid muscle of the cat, and mononeuronal innervation with peripheral branching of a single axon. We are not aware of any demonstration of multiple motor end plates on single muscle fibers of the canine larynx, although the histology of the canine vocal fold is not as well studied as that of the human one. Martensson[26] did not find any certain evidence for polyneuronal innervation in the canine thyroarytenoid muscle. These different arrangements of motor end plates may be expected to react differently in regard to the phenomena of fatigue; it may be that human vocal fold muscles have in this sense a higher safety factor than the canine ones. Furthermore, in the human thyroarytenoid muscle, a majority of the slower, probably more fatigue-resistant type 1 fibers would appear to be supplied with a pattern of multiple motor innervation that would make them particularly resistant to failure of neuromuscular transmission.

If we wish to extrapolate our findings to the function of the larynx in human phonation, it must be kept in mind that the conditions of voice production differ in important ways from those of ordinary respiratory activity. Hiroto et al[27] and more recently Matsuo et al[28] have found that the circulation of blood to the vibrating vocal fold actually decreases during phonation. This is the opposite of what is expected in ordinary muscle function, since below tetanic levels of contraction the blood flow to a muscle usually increases with its level of activity; this effect is more pronounced in muscles with a well-developed oxidative metabolism, such as those of the larynx.[29,30]

Whatever the cause of the decrease in blood flow to the vocal folds during phonation, the direction of the effect is predictable. The muscle will be forced to rely more on anaerobic metabolism, which is less fatigue-resistant than aerobic metabolism. Thus, the special conditions of phonation may make vocal fold muscles less resistant to fatigue in phonation than they are in other functions such as respiration.

On the other hand, the intriguing possibility may be considered that some particular styles of phonation minimize this effect, for instance by minimization of the collision stresses of the vocal folds. This is an area of considerable interest to singers, clinicians, and those who treat the professional voice. Other, more urgent questions also must be answered in regard to the effects of necessary laryngeal surgery on the fatigue resistance of laryngeal muscles, and the response of these muscles in such applications as long-term laryngeal pacing.

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Ann Otol Rhinol Laryngol 99:1990

IMAGING CASE STUDY OF THE MONTH

ADULT RHABDOMYOMA OF THE BASE OF THE TONGUE

HOWARD K. NAM, MD
MICHAEL A. MIKHAEL, MD
ALLAN P. WOLFF, MD
CHICAGO, ILLINOIS

PATIENT

An 85-year-old man presented with a sensation of a lump in the throat that had persisted for a 2-month period. The patient also reported a history of increasing dysphagia and dyspnea without associated pain or weight loss. Physical examination revealed a large, fleshy mass at the base of the tongue, partially obstructing the pharyngeal airway. An indirect examination showed a massive lobulated tumor that completely occluded the epiglottis.

RADIOGRAPHIC FINDINGS

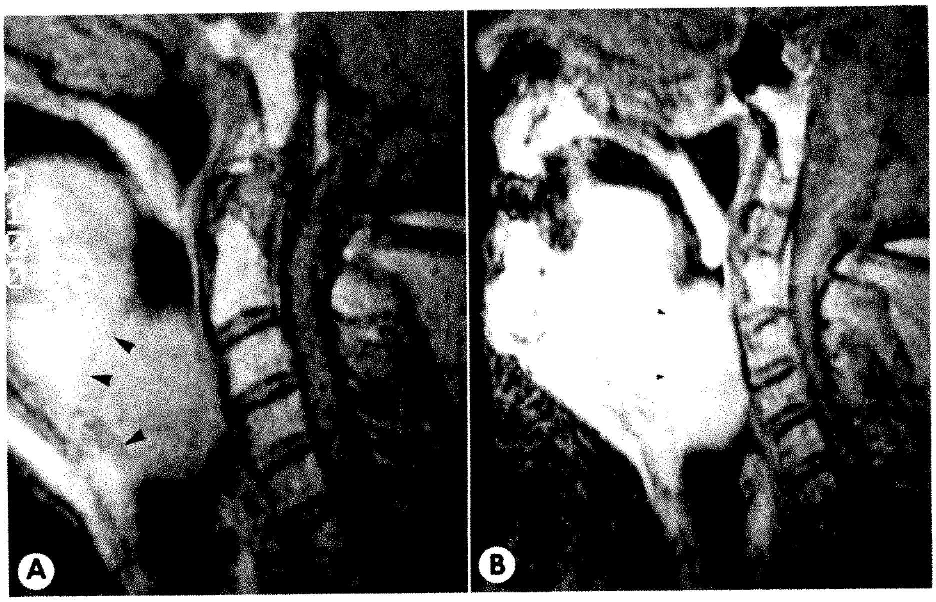
Magnetic resonance imaging with spin echo technique using short and long sequences (TR 600 to 2,000 ms and TE 20 to 70 ms) demonstrated a large, solid mass mushrooming from the base of the tongue and filling the oropharynx. The sagittal cuts (see Figure) revealed a line of cleavage between the tumor mass and the base of the tongue, indicating no radiographic evidence of infiltration. The posterior pharyngeal wall was also intact, with no evidence of invasion. The vallecula and epiglottis were obscured completely by the mass (see Figure, A). The long-sequence images clearly showed the homogeneous mass with the same soft tissue density as the tongue (see Figure, B). There was no lymph node involvement in the neck.

DIAGNOSIS

A biopsy of the mass revealed an adult rhabdomyoma. The patient underwent a local tracheostomy, a mandibular split, and a complete local excision of the tumor from the base of the tongue. The soft, reddish brown mass was well encapsulated and lobulated, measuring 7 cm in its greatest diameter. The final histologic diagnosis was consistent with the initial biopsy result.

DISCUSSION

Extracardiac rhabdomyoma is a benign neoplasm of skeletal muscle origin that is subdivided into fetal and adult types. The fetal rhabdomyomas have a predilection for the postauricular region in infants and the vulvovaginal region of adult women.[1,2] The adult rhabdomyomas are found most frequently in the head and neck region (approximately 95%), including the floor of the mouth, tongue, soft palate, submandibular region, and larynx.[2,3] The tumor oc-



Sagittal magnetic resonance imaging scan. A) Mass mushrooming from base of tongue abutting on posterior pharyngeal wall (TR 600 ms, TE 20 ms). Note line of cleavage (arrowheads) and lack of evidence of infiltration into tongue. B) Long-sequence image showing homogeneous solid mass with same signal intensity as tongue (TR 2,000 ms, TE 70 ms). Epiglottis is obscured by tumor. Note again line of cleavage (arrowheads).

From the Divisions of Otolaryngology–Head and Neck Surgery (Nam, Wolff) and Neuroradiology (Mikhael), Evanston Hospital and Northwestern University School of Medicine, Chicago, Illinois.

curs in persons of middle age and older with a nearly 5:1 male predominance. Histologically, the tumor is composed of large, polygonal eosinophilic muscle cells with well-formed cross-striations and intracytoplasmic glycogen vacuoles. It is not associated with an aggressive local growth or a malignant degeneration.

The adult rhabdomyoma often presents as a painless mass causing a sensation of a lump in the throat. Because of its slow growth, the tumor may not produce any significant symptoms until a partial obstruction of the upper aerodigestive tract occurs, causing dyspnea and dysphagia.

Contrast-enhanced computed tomography may be of value in the preoperative assessment. Magnetic resonance imaging, however, is superior in demonstrating the benign, solid tumor with a homogeneous soft tissue density. It also demarcates the mass well from the adjacent anatomic structures. In the differential diagnosis, lymphoma, rhabdomyosarcoma, and granular cell tumor should be considered. Magnetic resonance imaging findings discount the possibility of an aggressive malignant tumor. A definitive histopathologic diagnosis is made on a biopsy.

Treatment of adult rhabdomyoma is by a complete excision, at times necessitating a more aggressive surgical approach, as was used in this case. A long-term follow-up is essential, since local recurrences do occur.[4]

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CALL FOR PAPERS
SECOND INTERNATIONAL COCHLEAR IMPLANT SYMPOSIUM

The University of Iowa Department of Otolaryngology–Head and Neck Surgery and the International Cochlear Implant Association will hold the Second International Cochlear Implant Symposium in Iowa City on June 4-9, 1990. The symposium will focus on basic science aspects of electrical stimulation on the auditory system, new cochlear implant strategies, clinical application in both adults and children, and rehabilitation and educational issues. Please submit abstracts to Bruce J. Gantz, MD, Department of Otolaryngology–Head and Neck Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Ann Otol Rhinol Laryngol 99:1990

PATHOLOGY CONSULTATION

UNDIFFERENTIATED CARCINOMA WITH LYMPHOID STROMA OF THE MAJOR SALIVARY GLANDS

KAREN R. CLEARY, MD JOHN G. BATSAKIS, MD

HOUSTON, TEXAS

Undifferentiated carcinoma with lymphoid stroma or lymphoepithelial carcinoma of the major salivary glands is a demographically and histopathologically unique malignancy. Although whites may have the disease, it is preponderantly a carcinoma of North American Eskimos and native Greenlanders. The carcinoma shares many features with undifferentiated nasopharyngeal carcinomas, from which it must be distinguished: histologic appearance, putative relationship with Epstein-Barr virus, predilection for mongoloid races, and response to therapy. In some cases, the carcinoma appears to have evolved from a lymphoepithelial lesion.

World statistics on malignant salivary gland tumors are quite uniform in their presentations: less than 1% of all human cancer and an incidence that seldom exceeds 2.0 in 100,000 per year.[1] The dramatic exception to these data is the demographically and histopathologically unique undifferentiated carcinoma with lymphoid stroma or lymphoepithelial carcinoma. Its striking prevalence among native Greenlanders and the North American Inuit (Eskimo) is testimony to this. Indeed, a sobriquet for the neoplasm is "Eskimoma."

Malignant neoplasms of the parotid gland in Greenland comprise over 60% of all tumors of that gland, a frequency that is two to three times higher than that reported from other parts of the world.[1,2] An estimated annual incidence of 3.9 in 100,000 for males and 7.7 in 100,000 for females further accounts for their relatively high ranking among other forms of cancer in Greenland (Table 1[2]). Over 90% of the salivary gland malignancies occur in the parotid gland, and over 90% are undifferentiated carcinomas with lymphoid stroma.[1-3] Canadian Eskimos have been shown to have an incidence of salivary gland malignancy that is 30 times over the expected rate, with the majority also classified as undifferentiated carcinomas with lymphoid stroma.[4,5]

TABLE 1. MALIGNANT NEOPLASMS IN GREENLAND (1965-1977)

Site of Neoplasm	*No. of Cases*
Uterine cervix	170
Lung	133
Breast	70
Esophagus	57
Lymphoid and hematopoietic	36
Rectum	32
Prostate gland	3
Nasopharynx	49
Salivary glands	28

From data presented by Imperato.[2]

Mongoloid ethnicity is certainly a risk factor for this salivary carcinoma (Table 2[3]). Greenlanders, North American Eskimos, and Southern Chinese living in Hong Kong make up nearly three fourths of the reported cases. Whether the number of Hong Kong Chinese patients is an aberration of reporting is unclear. The incidence for major salivary gland cancer in that population is low — 1.0 per 100,000 males and 0.7 per 100,000 females — and is in sharp contrast to the high incidence of nasopharyngeal carcinoma.[3]

Reporting idiosyncrasy aside, existing data for these two geographically separate, ethnically related populations place them together for undifferentiated carcinomas of salivary glands and nasopharyngeal carcinomas. Nielsen et al[1] found the occurrence of nasopharyngeal carcinomas among native Greenlanders to be among the highest in the world: 12.3 per 100,000 males and 8.5 per 100,000 females. As with their Southern Chinese counterparts, the preponderant histopathologic type of

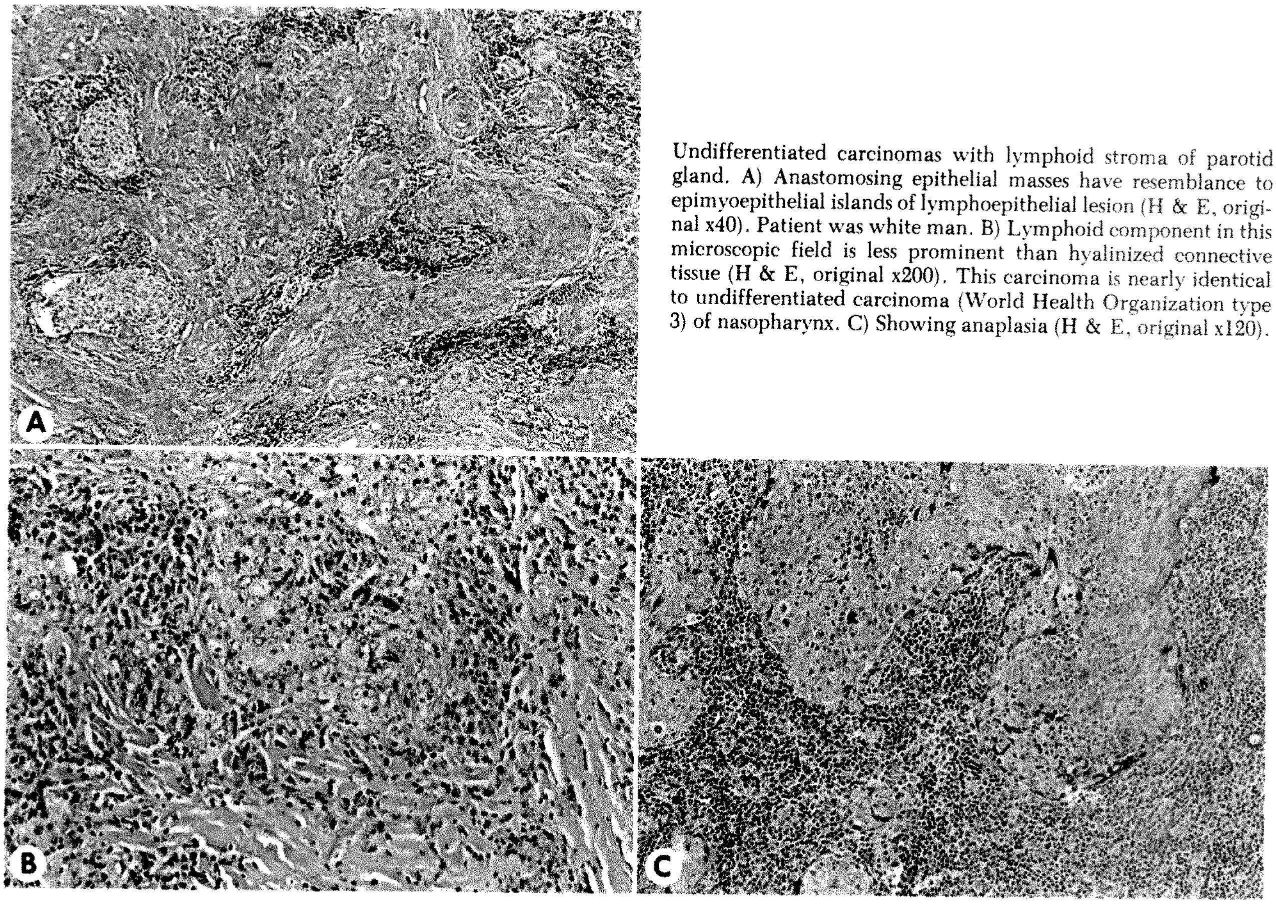
TABLE 2. UNDIFFERENTIATED CARCINOMA WITH LYMPHOID STROMA OF MAJOR SALIVARY GLANDS

	No. of Cases
Anatomic site	
Parotid gland	67
Submandibular gland	12
Unstated	1
Ethnic status of patients	
Greenlander-Eskimo	42
Southern Chinese	16
White	9
Indian	2
Japanese	2
Black	2
Anglo-Chinese	1
Unstated	6

From data presented by Saw et al.[3]

From the University of Texas M. D. Anderson Cancer Center, Houston.

REPRINTS — John G. Batsakis, MD, Division of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.



Undifferentiated carcinomas with lymphoid stroma of parotid gland. A) Anastomosing epithelial masses have resemblance to epimyoepithelial islands of lymphoepithelial lesion (H & E, original x40). Patient was white man. B) Lymphoid component in this microscopic field is less prominent than hyalinized connective tissue (H & E, original x200). This carcinoma is nearly identical to undifferentiated carcinoma (World Health Organization type 3) of nasopharynx. C) Showing anaplasia (H & E, original x120).

nasopharyngeal carcinomas in Greenlanders is the undifferentiated carcinoma or type 3 of the World Health Organization's classification.[6]

The salivary gland carcinomas and nasopharyngeal carcinomas are further linked by their putative association with the Epstein-Barr virus (EBV). Patients with undifferentiated salivary gland carcinoma with lymphoid stroma have demonstrated a familial clustering,[7] have shown enhanced antigenic stimulation as evinced by EBV-specific serum antibody titers, and have had EBV genome equivalents demonstrated in their salivary gland carcinomas.[8]

Claimed to be indistinguishable from nasopharyngeal carcinoma by either light or electron-optic studies,[9] the undifferentiated carcinoma with lymphoid stroma of salivary glands can assume different architectural growth patterns: epithelial islands, anastomosing or syncytial masses, or cords and isolated cells, usually set in a lymphoid stroma (see Figure, A). In some areas the lymphoid component is minimal or replaced by fibrous connective tissue. Usually the carcinoma is demarcated from nonepithelial elements and can appear to be a malignant caricature of the epimyoepithelial islands seen in lymphoepithelial lesions of salivary glands. Foci of squamous differentiation may be found, but the overall histopathologic appearance is that of an undifferentiated carcinoma whose phenotypic expression ranges from rather large cells with vesicular nuclei and prominent nucleoli to spindle-shaped cells (see Figure, B). The degree of anaplasia also varies, from severe anaplasia with pleomorphic nuclei and numerous mitoses to a uniform cell population and rare mitoses (see Figure, C). Necrosis, perineoplastic reactive histiocytes, and a granulomatous reaction can also be seen. Given the undifferentiated state of the neoplasm, extension into lymphatics and nerves is not expected.

The major salivary glands appear to be the exclusive sites of origin for this undifferentiated carcinoma, with the parotid gland leading the submandibular gland by a 7:1 ratio. Bilateral parotid gland involvement has been reported. Women are affected more than men, and the age of patients at the time of diagnosis has ranged from 20 to 60 years.[1,3]

Regardless of the afflicted population, it is obligatory to exclude a metastasis from the nasopharynx or Waldeyer's's ring epithelium when presented with an undifferentiated carcinoma with lymphoid stroma of the parotid or submandibular gland. As noted, EBV antibody titers may not be able to assist in the differential diagnosis. Catchment areas of parotid lymph nodes include the nasopharynx and oropharynx, but unilateral parotid swelling as a presenting sign of a nasopharyngeal carcinoma is very unusual, and parotid node involvement in known nasopharyngeal carcinomas is uncommon.[10]

Most of the patients with this carcinoma have been treated with a combination of surgical removal of the salivary gland (with or without neck dissection) and irradiation. Each of the modalities has also been used alone.[3,4]

Early metastasis to regional lymph nodes is a feature of the undifferentiated carcinoma with lymphoid stroma. At least 40% of patients are said to have histologically proven nodal metastases at their first presentation to a physician.[3] Local recurrence and systemic spread of disease have been recorded in 20% to 50% of patients.[3]

Clinical stage of disease is a major factor in response to therapy and survival.[4] Facial nerve dysfunction has not correlated with a poor outcome, but certain histopathologic features have.[4] A high mitotic rate, marked anaplasia, necrosis, and areas that simulate lymphoma are adverse findings. Favorable indicators are spindling of tumor cells and areas resembling lymphoepithelial lesions. Patients with advanced disease and aggressive cytomorphology have a high incidence of lymph node metastasis, have more recurrences, and usually die of the disease within 2 years.[4] Others, without these manifestations, have survived 5 years or longer without evidence of recurrent disease.[4]

Whether lymphoepithelial lesions are precursors to undifferentiated carcinomas with lymphoid stroma continues to be debated.[11,12] In our opinion, the coexistence of benign lymphoepithelial islands and the carcinoma, without histologic transition between the two, is not histogenetic evidence. The occasional case of documented lymphoepithelial lesion followed temporally by undifferentiated carcinoma with lymphoid stroma remains the strongest evidence that a few of the carcinomas have a benign progenitor.[13]

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SIXTH WORLD CONGRESS IN ULTRASOUND

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OBITUARY

JUERGEN TONNDORF, 1914-1989

Juergen Tonndorf, MD, former Director of the Fowler Memorial Laboratory for Research in Otolaryngology in the Department of Otolaryngology at Columbia University and Professor Emeritus of Otolaryngology in the College of Physicians and Surgeons of Columbia University, died at his home in Riverdale, New York, on Nov 3, 1989. He was 75 years old.

Born in Göttingen, Germany, the son of a professor of otolaryngology at Leipzig (Woldemar Tonndorf), Dr Tonndorf received his medical education and otolaryngology training at the University of Kiel. During World War II, he served in the German navy as a captain in the submarine corps.

His research on the effects of increased atmospheric pressure on hearing brought him to the attention of the US Air Force. He was invited to the School of Aviation Medicine, Randolph Air Force Base, Tex, in 1947. In 1953, Dr Tonndorf moved to the University of Iowa as an assistant research professor in the Department of Otolaryngology. In 1962, he joined the Department of Otolaryngology of Columbia University as Director of Research. There he established an auditory physiology laboratory, which he directed until his retirement in 1982.

Dr Tonndorf combined great curiosity and extensive scientific and clinical knowledge with a prodigious capacity for hard work to produce a rich body of research achievements. He was the author or coauthor of 157 publications on subjects that ranged from cochlear mechanics to middle ear function after perforation of the tympanic membrane, and from the physics of sound to the inhibition of tinnitus. He collaborated with a varied and distinguished group of scientists, engineers, and physicians as well as students in audiology and otolaryngology. He had an extraordinary ability to choose appropriate research questions based on the training and interests of his co-workers. He designed projects for residents who had no previous scientific training that could be completed within a 4-month research block. He also conducted long-term projects on the mechanics of hearing, such as research on bone conduction, that extended for over 10 years with several collaborators.

Dr Tonndorf was the recipient of numerous awards and honors in the United States and Europe, including the Ludwig Haymann Award of the German Otolaryngology Society, the Certificate of Merit of the American Academy of Otolaryngology and Ophthalmology, the Award of Merit of the American Otological Society, Inc, the Guyot Prize of the University of Gröningen (the Netherlands), the Shambaugh Prize of the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum, and the Award of Merit of the Association for Research in Otolaryngology. The Symposium on Mechanisms of Hearing was held in his honor at Columbia University in 1980. He received an honorary doctorate in medicine from the University of Göttingen, the H. Fletcher Award of the New York League for the Hard-of-Hearing, and the Cothenius Medal of the Academy of Sciences of Germany. He was also a member of the Editorial Board of the *Annals of Otology, Rhinology & Laryngology*.

Dr Tonndorf enjoyed a rich and varied life in New York with his wife, Mechtild. He loved to sail and to entertain friends and colleagues on his boat. He took great pleasure in his wife's cello playing. Following his wife's death in 1985, his health had declined steadily.

Juergen Tonndorf was a serious man who could appear austere at times, yet he was kind and generous with his colleagues, students, and friends. He was always fair. He steadfastly refused to take professional conflicts personally. Dr Tonndorf never practiced medicine after arriving in the United States. His unique contribution was that he could move gracefully back and forth from clinical medicine to science. He influenced and inspired both clinicians and scientists. This skill is greatly needed in our field today, and he will be missed deeply.

Maxwell Abramson, MD

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The William F. House Lectureship: From temporal bone to skull base surgery. U. Fisch, MD

Radiographic differential diagnosis of petrous apex lesions. R. K. Jackler, MD

Unusual presentation and rare causes of facial palsy: diagnosis by modern imaging techniques. A. Kumar, MD; T. Grosch, MD; M. Mafee, MD; F. Civantos, MD

Magnetic resonance angiography: technique and skull base applications. J. T. McElveen, Jr, MD; W. J. Meisler, MD; T. M. Grist, MD; O. B. Boyko, MD, PhD

Magnetic resonance imaging of facial nerve during paralysis. T. Murphy, MD

Magnetic resonance imaging-guided fine needle aspiration for the diagnosis of lesions of the skull base. R. Wenokur, MD; J. Andrews, MD; L. Layfield, MD; E. Abemayor; W. Hanafee, MD; B. Jabour, MD; R. Lufkin, MD

Labyrinthine enhancement on gadolinium-MRI in patients with sudden hearing loss and vertigo: correlation with audiologic and electronystagmographic studies. A. S. Mark, MD; S. Seltzer, MD

Acoustic neuroma surgery: predictive criteria for hearing preservation. B. E. Hirsch, MD; B. MacDonald, MD; D. B. Kamerer, MD; L. Sekhar, MD

Auditory monitoring during acoustic neuroma removal. D. H. Slavit, MD; S. G. Harner, MD; C. M. Harper, MD; C. W. Beatty, MD

Cochlear nerve compound action potentials during cerebellopontine angle surgery. J. M. Nedzelski, MD; S. Stanton, MD; M. Cashman, MD; R. Harrison, MD; D. W. Rowed, MD

Hearing preservation in acoustic neuroma surgery — the extended middle fossa approach. W. F. House, MD; W. E. Hitselberger, MD; T. B. Malony, MD

Recurrent acoustic tumor after suboccipital removal. B. S. Thedinger, MD; C. K. Whittaker, MD; C. M. Luetje, MD

Near-total and subtotal resection of acoustic neuroma: a preliminary report. J. L. Kemink, MD; A. W. Langman, MD; J. K. Niparko, MD; M. D. Graham, MD

Cerebrospinal fluid leaks and meningitis in acoustic neuroma surgery. G. E. Bryce, MD; J. M. Nedzelski, MD; D. W. Rowed, MD; J. M. Rappoport, MD

Modified Rambo meatoplasty in translabyrinthine tumor removal. W. L. Meyerhoff, MD, PhD; P. S. Roland, MD; B. Mickey, MD

Facial nerve monitoring in acoustic tumor surgery. J. A. Kwartler, MD; W. M. Luxford, MD; J. Atkins, MD; C. Shelton, MD

Intraoperative monitoring for preservation of facial nerve function in cerebellopontine angle surgery. P. E. Hammerschlag, MD; N. L. Cohen, MD

Pregnancy and acoustic neuroma. R. K. Gaughn, MD; S. G. Harner, MD

Preservation of neural function in operating on tumors of the jugular foramen. R. A. Goldenberg, MD; G. Gardner, MD

Electron microscopic evaluation of glomus jugulare tumors. J. B. Farrior, MD

Posterior fossa dural arteriovenous malformations. P. S. Roland, MD; B. E. Mickey, MD; W. L. Meyerhoff, MD, PhD; D. Sampson, MD

Cranial nerve preservation in lesions of the jugular foramen. C. G. Jackson, MD; B. A. Thedinger, MD; R. A. Cueva, MD; M. E. Glasscock III, MD

Meningiomas of the jugular foramen. T. B. Molony, MD; D. Brackmann, MD; W. Lo, MD

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Auditory and vestibular function after vestibular neurectomy. H. Silverstein, MD; S. Rosenberg, MD

The correlation of facial electroneurography with degenerating motoneurons. N. J. Coker, MD; L. T. Wang-Bennet, PhD

Intrinsic vasculature of the labyrinthine segment of the facial nerve: implications for site of lesion in Bell's palsy. T. Balkany, MD; M. Fradis, MD; B. W. Jafek, MD

Cargile membrane: an adjunct for facial nerve anastomosis. J. A. Herzog, MD; H. Felix, PhD; A. Bohmer, MD; U. Fisch, MD

The effects of muscle relaxants on intracranial facial nerve electrical stimulation and monitoring. D. A. Chen, MD; E. J. Teeple, MD; R. M. Sutherland, MD; S. Weber, MD

Facial nerve paralysis secondary to chronic otitis media without cholesteatoma. L. A. Harker, MD; S. Pignatari, MD

Intratemporal facial nerve neuromas. R. J. Wiet, MD; G. M. Pyle, MD; D. R. Schramm, MD

Intratemporal facial nerve hemangiomas. C. Shelton, MD; D. E. Brackmann, MD

Hypoglossal-facial interpositional-jump graft for facial reanimation without tongue atrophy. M. May, MD; S. M. Sobol, MD

Management of traumatic facial nerve paralysis: an update. U. Fisch, MD

Prediction of auditory nerve survival using the electrical auditory brain stem response. R. C. Fifer, PhD; M. A. Novak, MD

The "plateau effect" of cisplatin-induced hearing loss. S. F. Myers, PhD; B. W. Blakley, MD; S. Schwan, MA; R. H. Mathog, MD

Arachnoid granulation cerebrospinal fluid otorrhea. R. R. Gacek, MD

A temporal bone study method to evaluate clinical diagnostic criteria: permeability of patencies of the fissula ante fenestram. R. I. Kohut, MD; R. Hinojosa, MD; J. H. Ryu, PhD

Western blot analysis of serum antibody to inner ear antigens in patients with idiopathic progressive bilateral sensorineural hearing loss. R. Moscicki; J. E. San Martin; K. J. Bloch; S. Rauch; J. B. Nadol, Jr, MD

Technique for transmission and immunoelectron microscopy of the human endolymphatic sac and vestibular epithelia. P. A. Wackym, MD; P. H. Ward, MD; W. F. House, MD; F. H. Linthicum, Jr, MD; P. E. Micevych, PhD

Management of temporal bone carcinomas: a therapeutic analysis of two groups of patients and long-term follow-up. J. G. Spector, MD

Aggressive papillary tumors of the temporal bone. D. S. Poe, MD

Techniques of and reconstruction following temporal bone resection. M. L. Pensak, MD; K. A. Shumrick, MD

Functional ultrastructure of the inner ear in experimental hydrops. J. E. Veldman, MD; F. W. J. Albers, MD; E. H. Huizing, MD

Secondary endolymphatic hydrops. A. Shulman, MD

The exacerbation of symptoms in Meniere's disease during the premenstrual period. G. A. Ator, MD; J. C. Andrews, MD; V. Honrubia, MD

The therapeutic use of histamine in cochleovestibular disorders. M. M. McBrien, MD; J. C. Clemis, MD

Bilateral Meniere's disease in surgical versus nonsurgical patients. H. Silverstein, MD; S. Rosenberg, MD; J. Flanzer, MD

Endolymph pressure in Meniere's disease. J. J. Shea, MD

The surgical management of labyrinthine fistulas caused by cholesteatoma. S. C. Parisier, MD

Posterior semicircular canal occlusion in the normal hearing ear. L. S. Parnes, MD; J. A. McClure, MD

Repair of a perilymph fistula primarily through the middle ear and secondarily by occluding the cochlear aqueduct. D. J. Weider, MD

Implanted children's performance on tests of speech perception and lipreading ability. J. J. Shea III, MD; E. A. Domico, MS

Effects of chronic electrical stimulation on patients using a cochlear prosthesis. S. B. Waltzman, PhD; N. L. Cohen, MD; W. H. Shapiro, MA; R. A. Hoffman, MD

Results of functional evaluation with the Ineraid multichannel cochlear implant in optimal, difficult, and prelingual cases. P. Montandon, MD; M. Pelizzone, MD; A. Kasper, MD; A. Rohr, MD; P. Janssen, MD

Comparison of speech perception abilities in deaf children with hearing aids and cochlear implants. R. T. Miyamoto, MD; M. J. Osberger, PhD; A. M. Robbins, MS; W. A. Myres, MA

Facial nerve activation with cochlear implants. J. K. Niparko, MD; N. J. Coker, MD; N. L. Cohen, MD

Delayed extrusion of the Nucleus multichannel cochlear implant. R. A. Hoffman, MD; E. Goldofsky, MD; N. L. Cohen, MD; S. Waltzma, PhD; W. Shapiro, MA

Extracochlear stimulation with osseointegrated titanium implants. J. K. Niparko, MD; B. E. Pfingst, PhD; J. L. Kemink, MD

Electromagnetic ossicular replacement prosthesis — update. J. M. Kartush, MD; T. M. McGee, MD; M. D. Graham, MD; M. J. LaRouere, MD; K. C. Kulick, MA

KTP laser stapedotomy: is it safe? L. J. Bartels, MD

Transcanal infracochlear approach to the petrous apex. N. A. Giddings, MD; J. A. Kwartler, MD; D. E. Brackmann, MD

AMERICAN RHINOLOGIC SOCIETY

Saturday, April 28 (all day)

Diagnosis of allergy in disturbances of the nasal mucosa. D. Nalebuff, MD

Role of the autonomic nervous system and mediators of inflammation in rhinitis. J. Bernstein, MD, PhD

The mechanism of action of commonly used nasal drugs. Part I: decongestants, antihistamines, atropine; Part II: topically active drugs including cocaine. R. Jackson, PhD

Electron microscopy of the nasal mucosa in allergy and idiopathic vasomotor rhinitis. V. Jahnke, MD

Sinusitis-triggered rhinopathy. M. Berringer, MD

Modern management of the inferior turbinate in nasal obstruction. Round table. F. Lucente, MD (moderator); E. Kern, MD; H. Levine, MD; R. Mabry, MD; D. Nalebuff, MD (panelists)

Endoscopic sinus surgery: endangered species or thriving youth? M. Levitats, MD (moderator)

Surgical implication of embryology and developmental anatomy of the nose. A. Hengerer, MD

Management of nasal profile — options for reduction and augmentation. K. Calhoun, MD

Esthetic and functional impact of nasal tip surgery. F. Lopez Infante, MD

The understanding and correction of the crooked nose. D. Ellis, MD

Skeletal and soft-tissue surgery of the ethnic nose. F. Stucker, MD

Special problems in surgery of the nose. Round table. P. Arbour, MD (moderator); K. Calhoun, MD; D. Ellis, MD; A. Hengerer, MD; L. Neiman, MD; F. Stucker, MD (panelists)

AMERICAN OTOLOGICAL SOCIETY, INC

Saturday, April 28 (afternoon); Sunday, April 29 (morning)

Further studies on the effects of MRI fields on middle ear implants. E. L. Applebaum, MD; G. E. Valvassori, MD

Cochlear implant as a contraindication to MRI. W. M. Portnoy; K. F. Mattucci

Acoustic and elastic properties of middle ear prosthetic material. A. R. Eden, MD; A. S. Akers, MD; R. Chow, MD; J. L. Katz, MD

Facial nerve and deep petrous bone cholesteatomas. L. J. Bartels, MD

Diagnosis and treatment of giant cholesterol cyst of the temporal bone. E. Goldofsky, MD; R. A. Hoffman, MD; R. Holliday, MD; N. L. Cohen, MD

Contemporary management of neurofibromatosis. R. T. Miyamoto, MD; R. L. Campbell, MD; K. L. Roos, MD; R. M. Worth, MD

A TNM staging proposal for external auditory meatus carcinoma based on preoperative clinical examination and CT scan findings. M. Arriaga, MD; H. Curtin, MD; H. Takahashi, MD; B. Hirsch, MD; D. Kamerer, MD

Studies of cochlear blood flow in the human. J. M. Miller, PhD; G. Bredberg, MD; R. Grenman; J. Suonpaa; A. Didier

An animal model for human metabolic hearing loss in biotinidase deficiency. L. P. Rybak, MD; C. Whitworth; V. Scott

Transforming growth factor B: Does it direct otic capsule formation? T. R. Van De Water, PhD; D. A. Frenz; Galinovic-Schwartz

Noninvasive diagnosis of experimental endolymphatic hydrops by means of a low-frequency sound. T. Morizono, MD; R. Margolis, PhD; D. Lilly, PhD; S. Levine, MD; T. Tono, MD; N. Sano, MD; M. Rhodes

Cellular changes of Reissner's membrane in endolymphatic hydrops. T. H. Yoon, MD; M. Paparella, MD

Immunosuppression therapy in labyrinthitis induced by cytomegalovirus. G. L. Darmstadt; E. M. Keithley, PhD; J. P. Harris, MD, PhD

Autoimmune inner ear disease 1990 report. G. B. Hughes, MD; B. P. Barna, MD; S. E. Kinney, MD; L. H. Calabrese, MD; A. Koo, MD; N. J. Nalepa, MD

Idiopathic sudden sensorineural hearing loss and postnasal viral labyrinthitis: a statistical comparison of temporal bone findings. J. B. Nadol, Jr, MD; U. Khetarpal, MD; R. Glynn, PhD

Sudden hearing loss due to perilymphatic fistulae II: quantitative temporal bone histopathologic study. R. Hinojosa, MD; R. I. Kohut, MD; J. H. Ryu, PhD

Patterns of physical and sexual abuse of communicatively handicapped children. P. E. Brookhouser, MD; P. M. Sullivan, PhD; J. M. Scanlan, MD

Titration streptomycin therapy for bilateral Meniere's disease: follow-up report. A. W. Langman; J. L. Kemink, MD; M. D. Graham, MD

Bilateral semicircular canal aplasia with normal cochlear function: two case reports. L. S. Parnes, MD; W. G. Chernoff

A comparison of facial nerve monitoring systems in cerebellopontine angle surgery. J. R. E. Dickins, MD; S. Graham, MA

Facial nerve monitoring and otologic surgery: clinical indications and intraoperative technique. J. P. Leonetti, MD; G. J. Matz, MD; D. L. Beck, MA

Cochlear implants, tactile aids, hearing aids: a comparative study of their effectiveness for profoundly deafened children. J. A. Herzog, MD; A. Geers, PhD

Endoscopy of the cochlea during cochlear implantation. T. Balkany, MD

Cochlear implant complications. S. Parisier, MD; M. H. Weiss, MD; P. M. Chute, MA; S. A. Hellman, MS; R. Wang, MD; S. Selesnick, MD

Auditory brain stem implant: tumor size, preoperative hearing and benefit. S. R. Otto; W. F. House, MD; D. E. Brackmann, MD; W. E. Hitselberger, MD

The percutaneous pedestal in cochlear implantation. J. L. Parkin, MD

Direct electrical promontory stimulation to evoke electrical potentials of the auditory pathways: clinical application. J. L. Pulec, MD; J. C. Smith, PhD; M. L. Lewis, MA

AMERICAN LARYNGOLOGICAL ASSOCIATION

Saturday, April 28 (morning); Sunday, April 29 (afternoon)

The place of partial laryngectomy in the treatment of cancer — a view from the United Kingdom. H. J. Shaw, MD

Surgically treated early supraglottic cancer (T1 and T2). L. W. DeSanto, MD

Laser surgery for the treatment of laryngeal carcinomas. Indications, techniques and preliminary results. H. E. Eckel, MD; W. F. Thumfart, MD

Endoscopic laser exploration of supraglottic cancer. S. M. Zeitels, MD; C. W. Vaughan, MD

Medical complications in total laryngectomy: incidence and risk factors. M. A. Arriaga, MD; K. T. Kanel, MD; J. T. Johnson, MD; E. N. Myers, MD

Nonclosure of pharyngeal muscle after total laryngectomy. N. R. Olson, MD; L. Callaway, MS-CCC

The use of the nasogastric tube after total laryngectomy: is it truly necessary? F. Aprigliano, MD

Scintigraphy and aspiration pneumonia in head and neck cancer patients. K. L. Gwinn, MD; R. J. Nelson, MD; J. Muz, MD

Treatment of intractable aspiration using a laryngeal stent or obturator. E. C. Weisberger, MD

Sixteenth Daniel C. Baker, Jr, Lecture: The surgical management of supraglottic cancer and its metastasis in a conservative perspective. E. Bocca, MD

Glottic and supraglottic contributions to pitch raising. A videoendoscopic study. E. Yanagisawa, MD; J. Estill, MA; L. Mambrino, MD

Quantification of dynamic electromyographic and kinematic activity of the human vocal tract. R. Roark, PhD; S. D. Schaefer, MD; B. Watson, PhD; G. Kondraske, PhD; F. Freeman, PhD; L. Close, MD; M. Devous, PhD; T. Finitzu, PhD; K. Pool, MD

Botulinum toxin therapy for the treatment of laryngeal dystonia. A. Blitzer, MD, DDS; M. F. Brin, MD

Unilateral versus bilateral intralaryngeal injection of botulinum toxin for neurogenic adductor spastic dysphonia. R. J. Lipton, MD; T. V. McCaffrey, MD; A. E. Aronson, PhD; W. J. Litchy, MD

Spasmodic dysphonia: mechanism of failure of recurrent laryngeal nerve section. J. L. Netterville, MD; R. E. Stone, PhD; C. Rainey, MS; D. L. Zealear, PhD; R. H. Ossoff, DMD, MD

Five- to 14-year follow-up on 300 spastic dysphonia patients treated with recurrent laryngeal nerve section. H. H. Dedo, MD; M. S. Behlau, PhD

Histologic evaluation of the larynx in sudden infant death syndrome. D. F. N. Harrison, MD, PhD

Tracheotomy in the first year of life. G. J. Gianoli, MD; R. H. Miller, MD; J. L. Guarisco, MD

The ontogeny of the human cricoid cartilage. J. A. Tucker, MD

Laryngeal and tracheobronchial features of ligneous conjunctivitis. S. R. Cohen, MS, MD

Type I thyroplasty versus arytenoid adduction in the in vivo canine model. D. C. Green, MD; G. S. Berke, MD; T. S. Bell, PhD; V. F. Honrubia, MD; M. Natividad

Combined laryngeal framework medialization and reinnervation for unilateral vocal fold paralysis. H. M. Tucker, MD

Teflon, thyroplasty, or nerve transfer for laryngeal paralysis: a comparison. R. L. Crumley, MD

Electrical pacing for a dynamic treatment of unilateral vocal cord paralysis. H. Kojima, MD; K. Omori, MD; M. Nonomura, MD; I. Honjo, MD; N. Isshiki, MD; Y. Shimizu, MD

Transcutaneous intrafold injection for unilateral vocal fold paralysis. M. Hirano, MD; S. Tanaka, MD; Y. Tanaka, MD; S. Hibi, PhD

Microscopic intralaryngeal laryngoplasty without stent for bilateral vocal cord fixation. M. Rontal, MD; E. Rontal, MD

Endoscopic laser arytenoidectomy revisited. R. H. Ossoff, DMD, MD; J. A. Duncavage, MD; S. M. Shapshay, MD; Y. P. Krespi, MD; G. A. Sisson, MD

Laryngeal framework reconstruction with rigid miniplates. P. Woo, MD

Arytenoid subluxation: diagnosis and treatment. An integrated approach employing MRI, CT, videolaryngoscopy, EMG and laryngeal framework surgery. H. T. Hoffman, MD; J. A. Brunberg, MD; P. Winter, MD; M. J. Sullivan, MD; P. R. Kileny, MD

Epiglottic laryngoplasty for repair of blunt laryngopharyngeal trauma. B. L. Wenig, MD; J. A. Schild, MD; M. F. Mafee, MD

Surgical treatment of laryngeal web. N. Isshiki, MD; T. Taira, MD; K. Nose, MD; H. Kojima, MD

Reconstruction of the lye-burned larynx. M. Friedman, MD; V. T. Grybauskas, MD; T. K. Venkatesan, MD

Management of adult subglottic stenosis. T. McCaffrey, MD, PhD; T. Wang, MD; T. Koval, PhD; J. Earle, MD

Laryngeal chondrosarcomas: incidence, biological behavior, pathology, and treatment. A. Ferlito, MD

Immunohistochemical interpretation of early epithelial disorders in pyriform sinus. Y. Murakami, MD

Laser-resistant stainless steel endotracheal tube: experimental and clinical evaluation. M. P. Fried, MD; R. Mallampati, MD; F.-C. Liu, MD; S. Kaplan; D. S. Caminear; B. R. Samonte

AMERICAN SOCIETY FOR HEAD AND NECK SURGERY

Monday, April 30 (all day); Tuesday, May 1 (afternoon)

Detection of head and neck squamous cell carcinoma xenografts in nude mice by radiolabelled monoclonal antibody. J. J. Quak; M. Gerretsen; J. L. M. Meyer; G. A. M. S. van Dongen; G. B. Snow, MD, PhD

Drug response of head and neck tumors in native state histoculture. K. T. Robbins, MD; R. M. Hoffman, PhD; A. M. Storniolo, MD; H. Hoffman, MD; N. M. Varki, MD

The combined clinic — the best of all worlds, or management by committee? M. Spittle, MD

Systemic and local heparin in a microvascular arterial inversion graft thrombosis model. N. S. Jones, MD; M. G. Glenn, MD; L. Orloff, MS; M. M. Mayberg, MD

The lower island trapezius flap: a report of 35 cases. R. K. Naidu, MD; M. L. Urken, MD; W. Lawson, MD, DDS; H. F. Biller, MD

The inferior rectus abdominus myocutaneous free flap in head and neck reconstruction. M. L. Urken, MD; H. Weinberg, MD; C. Vickery, MD; J. Turk, MD; H. F. Biller, MD

Oromandibular reconstruction using microvascular composite free flaps: report of 60 cases. M. L. Urken, MD; C. Vickery, MD; H. Weinberg, MD; D. Buchbinder, DMD; W. Lawson, MD, DDS; H. F. Biller, MD

Mandibular reconstruction with osteocutaneous free flaps: histomorphology of bone union. H. T. Hoffman, MD; M. Sullivan, MD; S. Baker, MD; M. Ridley, MD

Medial maxillectomy for unilateral sinus neoplasms. J. D. Osguthorpe, MD; R. Weisman, MD

The value of manubrial resection in avoiding stomal recurrence. D. F. N. Harrison, MD, PhD

Circulating Clq binding macromolecules and its relationship to radiographic characteristics of laryngeal cancer. P. Lavedan; H. Savage, PhD; Y.-Y. Lee, MD; G. Young; S.-P. Schantz, MD

Mucosa-sparing total laryngectomy: indications and advantages. R. W. Bastian, MD; S. L. Collins, MD

Verrucous carcinoma of the larynx. G. L. O'Halloran, MD; T. V. McCaffrey, MD, PhD

Radiotherapy: the mainstay in the treatment of early glottic carcinoma. P. Pellitteri, DO; T. L. Kennedy, MD; D. P. Vrabec, MD; M. Hellstrom, MD; D. Beiler, MD

Continuous on-line monitoring of free-tissue transfers to the head and neck: use of an implantable combined pH/PO2 biosensor. D. B. Kuriloff, MD; J. Sullivan, MD

Sensate flaps for head and neck reconstruction — the next frontier. R. E. Hayden, MD

Vascularized and conventional interposition nerve grafts: a histomorphologic comparison in the rabbit. W. R. Carroll, MD; M. J. Sullivan, MD; M. Blaivas, MD, PhD; S. Rizk

Comparison of gastrostomy techniques in advanced head and neck cancer patients. C. Bailey, MD; J. R. Jacobs, MD; C. E. Lucas, MD; A. Ledgerwood, MD

Five-year results of cisplatin and 5-FU chemotherapy in the treatment of advanced resectable head and neck carcinoma — an RTOG report. J. R. Jacobs, MD; K. K. Fu, MD; L. D. Lowry, MD; R. L. Doggett, MD; M. Al-Sarraf, MD

The in-vivo biologic effect of interleukin-2 and interferon alpha on natural immunity in head and neck cancer patients. S. P. Schantz, MD; G. Clayman, MD; P. Lavedan; D. Taylor, MS; C. Pellegrino; H. Savage, PhD

A phase I-II trial of interferon gamma in head and neck cancer. W. J. Richtsmeier, MD, PhD; W. M. Koch, MD; P. McGuire, MD; E. Chang, PhD

Fibrinogen and acute phase proteins in head and neck cancer patients treated with interleukin-2. G. L. Clayman, MD; S. P. Schantz, MD; F. J. Liu, MD; R. Buchsbaum, MD; H. E. Savage, PhD; D. Taylor, MS; G. Young; T. Racz, MD; C. Pellegrino; J. M. Trujillo, MD; H. Goepfert, MD

Clinical application of anti-PCNA immunocytochemistry in soft-tissue sarcomas of the head and neck. M. D. Coltrera, MD; A. M. Gown, MD

Leiomyosarcoma of the sinonasal tract: a clinicopathologic study of nine cases. A. Kuruvilla, MD; B. M. Wenig, MD, CDR, MC, USNR; D. M. Humphrey, MD; D. K. Heffner, MD, Capt, MC, USN

Globus pharyngeus: long-term follow-up with prognostic factors. C. I. Timon, MD; T. O'Dwyer, MD

Chondrosarcoma of the head and neck: the UCLA experience 1955 to 1987. R. J. Mark, MD; L. M. Tran, MD; J. Sercarz, MD; T. C. Calcaterra, MD

Osteogenic sarcoma and fibrosarcoma of the head and neck. R. J. Mark, MD; L. M. Tran, MD; J. Sercarz, MD; T. C. Calcaterra, MD

Factors influencing survival in ethmoid sinus cancer. D. H. Kraus, MD; B. M. Sterman, MD; H. L. Levine, MD; B. G. Wood, MD; H. M. Tucker, MD; P. Lavertu, MD

Total or near-total glossectomy with laryngeal preservation for advanced carcinoma of the tongue. R. S. Weber, MD; L. Ohlms, MD; J. Bowman, MS; H. Goepfert, MD

Malignant tumors of the parotid gland. W. J. Kane, MD; T. V. McCaffrey, MD, PhD; K. D. Olsen, MD; J. E. Lewis, MD

Changes in Epstein-Barr virus–related antibody titers after therapy for nasopharyngeal carcinoma. H. B. Neel III, MD, PhD; G. R. Pearson, PhD; W. F. Taylor, PhD

Adenoid cystic carcinoma of submandibular gland: correlation of histologic features and prognosis with flow cytometric DNA analysis. A. El-Naggar, MD; M. A. Luna, MD; R. M. Byers, MD; H. Goepfert, MD

Adenoid cystic carcinoma of the hard palate. W. Kuhel; C. D. Wendt; H. Goepfert, MD

Facial translocation approach to cranial base. I. P. Janecka, MD; C. Sen, MD; L. Sekhar, MD; M. Arriaga, MD

The association of human papillomavirus with tonsillar carcinoma. R. A. Gallo, MD; S. A. McCormick, MD; F. E. Lucente, MD

Parathyroid autotransplantation during thyroid surgery. A. Shaha, MD; C. Burnett, MD; B. M. Jaffe, MD

Thyroidectomy under local anesthesia. M. Hochman, MD; W. E. Fee, MD

Photodynamic therapy in the treatment of squamous cell carcinoma of the head and neck. B. L. Wenig, MD; D. Kurtzman, MD; L. I. Grossweiner, PhD; D. M. Harris, PhD; R. Priez, RN; R. Lobraico, MD; E. L. Applebaum, MD

Early vascular events during photodynamic therapy utilizing chloroluminum tetrasulfonated phtalocyanine. S. J. Stern, MD; S. Jacques, PhD; S. Flock, PhD; S. Thompson, MD; S. Small; H. Goepfert, MD

The use of MRI to identify the extent of head and neck tumors. R. A. Hendrix, MD; P. Bloch, PhD; R. Lenkinski, PhD; W. G. McKenna, MD, PhD; M. Breyer, MD

Improving predictive values in cervical metastasis with CT and MRI. P. J. Hillsamer, MD; D. E. Schuller, MD; D. W. Chakeres, MD

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC

Tuesday to Thursday, May 1-3 (mornings)

Hypotympanum and infralabyrinthine cells in chronic otitis media. J. B. Nadol, Jr, MD

Congenital cholesteatoma of the middle ear in children: a clinical and histopathological report. T. J. I. McGill, MD; G. B. Healy, MD; E. M. Friedman, MD; S. Merchant, MD

The use of heterologous cartilage in tympanoplasty. C. W. Jansen, MD

Use of intraoperative ABR to guide prosthesis positioning. S. Levine, MD; S. Liston, MD; R. Margolis, PhD

A new middle ear implantable hearing aid. J. M. Fredrickson, MD; E. P. Wilson, MD

Auditory performance with simultaneous intracochlear multichannel stimulation. J. L. Parkin, MD; L. Randolph, MS

Results of cochlear implant reinsertion. S. C. Parisier, MD; P. Chute, MA; M. Weiss, MD; S. Hellman, MS; S. Selesnick, MD

Plasmapheresis in autoimmune inner ear disease. C. M. Luetje, MD

Cochleosacculotomy revisited: a good procedure in selected patients. N. A. Giddings, MD; C. Shelton, MD; M. J. O'Leary, MD; D. E. Brackmann, MD

Dynamic posturography findings associated with falls among the elderly. C. A. Bowman, MD

Chronic cough in infants and children: an update. L. D. Holinger, MD; A. Sanders, MD

Evaluation of neonatal subglottic stenosis: a 3-year prospective study. P. J. Nichlaus, MD; W. S. Crysdale, MD; S. Conley, MD; A. K. White, MD; V. Forte, MD

Lymphatic malformations of the head and neck in children. E. M. Friedman, MD; G. B. Healy, MD; T. J. I. McGill, MD

Endoscopic management of CSF leaks. D. E. Mattox, MD; D.

Kennedy, MD

Peritonsillar abscess: clinically effective and cost-effective treatment strategies. G. T. Simpson, MD; H. Herman, MD

The microbiological and histopathological changes in chronic ethmoiditis. J. D. Woodham, MB; P. W. Doyle, MD, FRCPC

The conservative management of paranasal sinusitis — contemporary analogy and re-evaluation of Dr Furstenberg's study, 1938-1990. B. S. Eichel, MD

Holmium laser-assisted endoscopic sinus surgery: laboratory experience. S. M. Shapshay, MD; E. E. Reibeiz, MD; R. K. Bohigian, MD; R. L. Hybels, MD

CO2 laser treatment in tongue carcinoma. M. Hirano, MD; T. Kawaguchi, MD

Ogura Lecture: Moral dilemmas in the management of head and neck cancer. D. F. N. Harrison, MD, PhD, FRCS

A new approach to microlaryngeal surgery. E. Kantor, MD; G. Berci, MD; E. Partlow; M. Paz-Partlow, MFA

Lipoinjection for unilateral vocal cord paralysis. D. O. Mikaelian, MD; L. D. Lowry, MD; R. T. Sataloff, MD

Electromyography of masticatory muscles in craniomandibular disorders. B. C. Cooper, DDS; D. L. Cooper, MD; F. E. Lucente, MD

Update: ansa-recurrent laryngeal nerve anastomosis for unilateral laryngeal paralysis. R. L. Crumley, MD

Head and neck trauma in taxis — a growing urban problem. A. Komisar, MD, DDS; S. M. Blaugrund, MD; M. Camins, MD

Fine needle aspiration biopsy of head and neck masses in infants and children: experience with 93 consecutive cases. D. L. Mobley, MD; P. E. Wakley, Jr, MD; M. A. Smith Frable, MD

LeFort osteotomy approach to the skull base. C. T. Sasaki, MD; R. Lowlicht, DDS; D. Astrachan, MD

The role of surgery in rhabdomyosarcoma of the head and neck in children. G. B. Healy, MD; P. M. C. L. Black, MD; J. Upton, MD

Esthesioneuroblastoma — surgical treatment without radiation. H. F. Biller, MD; V. P. Sachdev, MD; W. Lawson, MD, DDS; P. Som, MD

Squamous cell carcinoma of the head and neck in patients under 40 years of age. P. J. Martin, MD; C. Jacobs, MD; W. E. Fee, Jr, MD; D. Goffinet, MD

Selective management of early glottic cancer. R. K. Davis, MD; S. M. Kelly, MD; J. L. Parkin, MD; M. H. Stevens, MD; L. P. Johnson, MD

Carcinoma of the buccal mucosa: a 25-year analysis. G. Govett, MD; R. C. Amadee, MD

Idium-111 anti-CEA monoclonal for imaging head and neck malignancies. M. A. Walsh, MB, FRCSI; D. McShane, MB, FRCSI; C. Timon, MB, FRCSI; D. Hamilton, BSc, PhD

Melanoma of the head and neck. J. Conley, MD

Absorbable suture for laser-assisted microvascular anastomosis. M. P. Fried, MD; D. S. Caminear; E. R. S. Moll; B. R. Samonte

Assessment of myocutaneous flap viability in humans using MRI with paramagnetic contrast agents. P. W. Fling, MD; R. W. Dalley, MD; K. R. Maravilla, MD; R. M. Varnell, MD; C. W. Cummings, MD

Bone-inducing implants in head and neck surgery. D. M. Toriumi, MD; C. East, MD; D. Rosen, PhD; W. F. Larrabee, MD

Parameters for success in functional oromandibular reconstruction. M. L. Urken, MD; D. Buchbinder, DDS; A. Sheiner, DDS; H. Weinberg, MD; C. Vickery, MD; W. Lawson, MD, DDS; H. F. Biller, MD

The efficacy of comprehensive neck dissection with or without postoperative radiotherapy. G. B. Snow, MD, PhD; C. R. Leemans, MD; J. P. Nauta; R. M. Tiwari, MD, PhD

Hematoporphyrin photodynamic therapy: is there a future in head and neck oncology? Reflections on a 5-year experience. J. L. Gluckman, MD

AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

Wednesday and Thursday, May 2-3 (afternoons)

Arytenoidectomy in children. S. S. Choi, MD; R. T. Cotton, MD

Extraluminal arytenoid reconstruction: application of phonosurgical principles to glottic reconstruction. G. Isaacson, MD

Regulation of phonatory efficiency by vocal fold tension and glottic width in the excised canine larynx. D. H. Slavit, MD; T. V. McCaffrey, MD

Sulcus vocalis: functional aspects. M. Hirano, MD; T. Yoshida; S. Tanaka; S. Hibi

The evaluation of the laryngeal changes occurring during exercise and exercise-induced asthma. C. G. Hurbis, MD; J. Schild, MD

Tracheostomy in bone marrow transplant patients. C. B. Anderson, MD, DDS; G. L. Adams, MD; J. P. Neglia, MD

Percutaneous transtracheal delivery of oxygen for long-term continuous therapy. J. T. Johnson, MD; L. A. Hoffman, RN, PhD; S. W. Wesmiller, RN, MSN; F. C. Sciurba, MD; J. H. Dauber, MD

The effect of nasal packing and tracheotomy on pulmonary surfactant: a rabbit model. T. F. Dowling, MD; J. A. Koufman, MD

Management of laryngotracheal stenosis: long-term results. Y. P. Krespi, MD; G. Josephson; M. Goldsher, MD

Microtrapdoor repair of laryngeal and tracheal stenosis. D. J. Beste, MD; R. J. Toohill, MD

Tracheobronchopathia osteochondroplastica. D. M. Nienhuis, MD; U. B. S. Prakash, MD; E. S. Edell, MD

Surgical management of tracheal stenosis in an infant with multiple congenital anomalies. When is Baby inoperable? L. Mambrino, MD; M. A. Kenna, MD; J. Seashore, MD

Laser applications in the trachea and bronchi — Lahey Clinic Medical Center experience, 1982 to 1989. S. M. Shapshay, MD; J. F. Beamis, Jr, MD; E. E. Rebeiz, MD

Indications for Nd:YAG laser bronchoscopy. J. Werber, MD; S. Stein, MD; M. Nussbaum, MD

The Dohlman endoscopic diverticulotomy. F. M. Byl, MD; D. M. Wayman, MD

Neonatal and pediatric microsubglottiscope set. R. H. Ossoff, DMD, MD; J. A. Werkhaven, MD; J. A. Tucker, MD

A completely new approach to microlaryngeal surgery. E. A. Kantor, MD; G. Berci, MD; E. Partlow; M. Paz-Partlow, MFA

New pediatric laryngoscopes. Col David S. Parsons, USAF, MC

Endoscopic assessment of swallowing and aspiration. N. R. Olson, MD

The diagnosis and treatment of laryngeal cleft. C. Eriksen, MD; D. Zwillenberg, MD; N. Robinson, MD

Cautery-induced endotracheal tube ignition during tracheotomy. A. Aly, MD; M. McIlwain, DDS; J. A. Duncavage, MD

Bronchial foreign bodies — an uncommon way of entry. F. Aprigliano, MD

Vascular injury following foreign body perforation of the esophagus: review of the literature and report of a case. R. L. Scher, MD; C. J. Tegtmeyer, MD; W. C. McLean, MD

Unusual applications of ultrathin flexible bronchoscopes in pediatric surgical patients. R. E. Wood, PhD, MD; R. Azizkhan, MD; S. Lacey, MD; J. Sidman, MD; A. Drake, MD

Late pharyngoesophageal perforation: a complication of anterior spine surgery. M. F. Kelly, MD; J. Spiegel, MD; D. Zwillenberg, MD

Esophageal foreign bodies in children: a 15-year review. W. S. Crysdale, MD; K. Sendi, MD; P. Nicklaus, MD

Pitfalls in the diagnosis and management of foreign bodies. S. R. Cohen, MD

Management of tracheobronchial foreign bodies. G. B. Healy, MD

Removal of tracheobronchial foreign bodies by flexible bronchoscopy. D. R. Sanderson, MD

Removal of sharp and penetrating foreign bodies from the esophagus and stomach. L. D. Holinger, MD

Removal of blunt foreign bodies from the esophagus. D. B. Hawkins, MD

AMERICAN SOCIETY OF PEDIATRIC OTOLARYNGOLOGY

1990 Preliminary Program

(Subject to change)

Four Seasons Hotel, Toronto, Ontario

Thursday to Saturday, May 17-19 (mornings)

The prognostic value of endotracheal tube air leak following tracheal surgery in children. M. S. Godin, MD; A. B. Seid, MD; S. M. Pransky, MD; D. B. Kearns, MD; B. Peterson, MD

Cricoid quartersection versus anterior-posterior cricoid split: effects on subglottic growth. D. A. Foggia, MD; S. D. Gray, MD

Tracheal anastomosis in lambs: comparison of two sutures and two techniques. E. M. Friedman, MD; A. R. Perez-Atayde, MD; M. Silvera; R. A. Jonas, MD

External fixation using microplates after laryngotracheal expansion surgery — animal study. G. H. Zalzal, MD; E. S. Deutsch, MD

Reconstruction of the pediatric larynx and upper trachea with the sternohyoid myocutaneous flap (rotary door flap). I. Eliachar, MD; H. Tucker, MD

One-stage reconstructive laryngotracheoplasty. A. B. Seid, MD

Single-stage laryngotracheal reconstruction. S. D. Gray, MD; R. Lusk, MD; H. Muntz, MD

Evolving experience with laser therapy for lymphatic malformations of the upper aerodigestive tract. M. M. April, MD; S. M. Shapshay, MD; E. Rebeiz, MD; G. B. Healy, MD

Laryngeal cysts in the newborn. V. Forte, MD; J. Wailshawski, MD

The endoscopic repair of laryngeal clefts. P. J. Koltai, MD; D. Morgan, MB, FRCS; D. Mitchell, MD, FRCS; J. Evans, MD, FRCS

Tracheal granulation tissue — a study of bacteriology. B. H. Matt, MD; C. M. Myer III, MD; S. Reising, PhD; R. T. Cotton, MD

Pediatric sinusitis. K. Duplechaim, MD; R. Miller, MD

Refractory otitis and rhinosinusitis: manifestations of primary immunodeficiencies. S. C. Mauning, MD; O. E. Brown, MD; R. L. Wasserman, MD, PhD

Management paradigm for pediatric functional endoscopic sinus surgery candidates. J. R. Thomsen, MD; G. Milmoe, MD

Pediatric functional endonasal sinus surgery: review of 210 cases. R. H. Lazar, MD; C. W. Gross, MD; R. T. Younis, MD; M. J. Gurucharri, MD

Recurrence of sinus disease following endoscopic sinus surgery. D. S. Parsons, MD; E. A. Mair, MD; W. E. Bolger, MD

Ethmoidectomy in patients with immune deficiencies. R. P. Lusk, MD; S. H. Polmar, PhD, MD; H. R. Muntz, MD

ENT manifestations in primary immunodeficiencies in children. J. Haddad, Jr, MD; R. Brager; C. D. Bluestone, MD

Microbiology of chronic sinusitis. R. Park, MD; P. W. Orobello, MD; R. M. Naclerio, MD

Bacteriology of chronic sinusitis in children. H. R. Muntz, MD; R. P. Lusk, MD

Hyoid suspension to manage chronic aspiration in children. N. W. Todd, MD; H. Heindel, MD; F. M. S. McConnel, MD

Mandibular fractures in the pediatric patient. M. Siegel, MD; R. Wetmore, MD; L. Tom, MD; S. D. Handler, MD; W. P. Potsic, MD

Prenatal development of aerodigestive tract function revealed by ultrasonography. G. C. Isaacson, MD; J. C. Birnholz, MD

Mycobacterial cervical adenitis: medical and surgical management. A review of 65 pediatric cases. M. Shindo, MD; D. B. Hawkins, MD; E. J. Kahlstrom, MD; E. F. MacLaughlin, MD

Balloon dilatation of esophageal strictures in children. C. M. Myer III, MD; W. S. Ball, Jr, MD; G. S. Bissett III, MD

Changes in tonsil bacteriology: 1980 versus 1989. C. Timon, MB, FRCSI; M. Cafferkey; M. Walsh, MB, FRCSI

Actinomycosis in obstructive adenotonsillar hypertrophy and recurrent tonsillitis. S. Pransky, MD; J. I. Feldman, MD; D. B. Kearns, MD; A. B. Seid, MD; G. F. Billman, MD

Congenital interarytenoid web. B. N. Benjamin, MD; E. Mair, MD

Juvenile fibromatosis: hormonal receptors and histologic characteristics — the possible basis for a classification. J. Maddalozzo, MD; L. T. Tenta, MD; D. Morse, MD; L. Hutchinson, MD

Nodular fasciitis of the head and neck in children: a deceptive lesion. L. J. DiNardo, MD; R. F. Wetmore, MD; W. P. Potsic, MD

Respiratory papillomatosis: presentation before 6 months. F. L. D. McClurg, MD; B. Chipps, MD; E. Friedman, MD; G. L. Adams, MD

Prospective documentation of noncongenital hereditary hearing loss in children. N. Sculerati, MD; J. R. Madell, PhD

Inherited deafness in Waardenburg syndrome. K. M. Grundfast, MD

Effectiveness and efficiency of language screening in pediatric otorhinolaryngology. R. J. Ruben, MD

Screening audiometry in a level III nursery. P. Connolly, MD; A. Yelich, MA; S. Yerger, PhD; R. J. H. Smith, MD

Middle ear immune complexes in otitis media with effusion. J. F. Stanievich, MD; H. Faden, MD; J. Bernstein, MD; L. Brodsky, MD; M. Pizzuto, MD; D. Krystofik, RN; J. J. Hong; P. L. Ogra, MD

Late results of otolaryngologic care in cleft palate patients. S. D. Gray, MD; R. Miller, MD; M. Rohrs, MD

Cervicofacial cystic hygroma: predictors and patterns of postsurgical recurrence. E. J. Ricciardelli, MD; M. A. Richardson, MD

The sequelae of the Munchausen's syndrome by proxy as seen in a review of the ENT clinic patients at HSC. R. E. MacDonald, MD; J. Wittenberg, MD; H. Walker, RN

The dumbbell tumor of the cavernous sinus/infratemporal fossa. R. D. Eavey, MD; P. Janfaza, MD; P. Chapman, MD; B. Swearingen, MD

The transoropalatal approach in the pediatric population to the atlanto-axial region. W. Redmond, MD; V. Forte, MD

Thyroid scans in thyroglossal duct remnants. D. Radkowski, MD; T. J. I. McGill, MD; G. B. Healy, MD; J. Arnold, MD; S. T. Treves, MD; H. Paltiel, MD; E. M. Friedman, MD

Lowering the incidence of perforation following Goode T-tube removal. A. F. Inglis, Jr, MD; M. A. Richardson, MD

Postoperative salivary gland function by technetium scanning and submandibular duct diversion patients. A. J. Hotaling, MD; D. N. Madgy, DO

Prevention of recurrent cholesteatoma in intact canal wall mastoidectomy tympanoplasty. N. P. Redfield, MD; G. Church, PhD, CCC-A

Manhattan Eye, Ear & Throat Hospital

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OTHER PUBLICATIONS

Spastic Dysphonia: State of the Art 1984
Edited by George A. Gates, M.D.
Transcripts of Panel Discussion, International Symposium on the Larynx, University of California, School of Medicine, San Francisco, California. 42pp. Softbound $15.00 U.S.

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